Neurophysiological correlates of preparation for action measured by electroencephalography

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A thesis submitted to

The University of Birmingham

for the degree of

DOCTOR OF PHILOSOPHY

School of Psychology

The University of Birmingham

November 2008

Abstract

The optimal performance of an action depends to a great extend on the ability of a person to prepare in advance the appropriate kinetic and kinematic parameters at a specific point in time in order to meet the demands of a given situation and to foresee its consequences to the surrounding environment. In the research presented in this thesis, I employed high-density electroencephalography in order to study the neural processes underlying preparation for action. A typical way for studying preparation for action in neuroscience is to divide it in temporal preparation (when to respond) and event preparation (what response to make). In Chapter 2, we identified electrophysiological signs of implicit temporal preparation in a task where such preparation was not essential for the performance of the task. Electrophysiological traces of implicit timing were found in lateral premotor, parietal as well as occipital cortices. In Chapter 3, explicit temporal preparation was assessed by comparing anticipatory and reactive responses to periodically or randomly applied external loads, respectively. Higher (pre)motor preparatory activity was recorded in the former case, which resulted in lower post-load motor cortex activation and consequently to lower long-latency reflex amplitude. Event preparation was the theme of Chapter 4, where we introduced a new method for studying (at the source level) the generator mechanisms of lateralized potentials related to response selection, through the interaction with steady-state somatosensory responses. Finally, in Chapter 5 we provided evidence for the existence of concurrent and mutually inhibiting representations of multiple movement options in premotor and primary motor areas.

Acknowledgements

I would first like to thank my supervisor Dr. Peter Praamstra for his continuous guidance, sound advice and prompt responding whenever his input was necessary. I would also like to thank Prof. Alan Wing who, along with my supervisor, gave me the chance to start my degree and also for his important contribution in the early stages of my research.

Many thanks to Nick Roach for the technical/programming assistance and also to Dr. Hoi-Fei Kwok for sharing her MATLAB expertise with me and for the fruitful collaboration we had in the first two experiments of this thesis.

Special thanks to all the members of the SyMoN lab and mostly to Dr. Ellen Seiss and Dr. Paul Pope for their assistance in understanding the small but important aspects of EEG research.

My sincere thanks to all my participants (even to the ones who blinked) without whom this thesis would not have been possible.

Lastly, but more importantly, I would like to thank my family and all my friends who supported me and kept me on track throughout the course of my studies.

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Chapter 1

General Introduction

1.1. Preface

In this introductory section of the present thesis, we will first discuss the basic concepts of electroencephalography (EEG), its advantages and limitations and we will also present the basic tools employed in EEG analyses of neural mechanisms in motor control studies. Next, we will discuss the role of preparation for action as a function of reduction of "uncertainty" (see Section 1.4.). Then we will present various scientific views regarding the internal models that the central nervous system makes use of in anticipatory motor control and briefly discuss the methods employed by researchers in order to study the peripheral expressions of these models. Finally, we will discuss the most important brain areas involved in motor control (giving emphasis to cortical structures) and the movement- related EEG components, which were extensively studied in our experiments.

1.2. Electroencephalography

Electroencephalography (EEG) is a neurophysiological technique used for assessing central nervous system function and organization. In EEG, voltage fluctuations are recorded from the scalp, which result from ongoing/background brain electrical activity in combination with event-related activity, produced by the activation of multiple cortical and subcortical sources, triggered by external or internally generated events.

EEG is recorded from electrodes placed on the scalp in such a way as to have anatomical and functional relevance to the underlying cortical areas and to provide adequate coverage of the total head area. Electrode locations typically follow the

International 10-20 system convention (Jasper, 1958). This system places the electrodes at proportional distances (i.e. 10% and 20%) between anatomical landmarks of the skull and the head, along specific contour lines over the scalp. The technological advancement of multi-channel EEG led to the extended 10-20 system (Chatrian et al., 1985), which simply placed all the electrodes at 10% proportional distances. The need as well as the capability for denser electrode placements dictated the proposal of the 10-5 system or the 5% system (Oostenveld and Praamstra, 2001), where the electrodes are placed at 5% proportional distances.

1.2.1. Methodological Considerations

EEG is a well-established method for the real-time assessment of brain function. It provides precise information about when brain sources are activated, for how long and in which order. Nevertheless, there are limitations in this method, primarily the selection of an inactive site to which recorded activity can be referenced and most importantly its limited capabilities in identifying the exact locations from which the scalp-recorded activity originates.

1.2.1.1. The "Reference problem"

Local activities are recorded from "active" electrode sites with respect to activities recorded from neutral/"inactive" sites of the head (Nunez, 1981). The bridge of the nose,

the sternum and more frequently the earlobes and the mastoids have been used in EEG experiments as “quiet reference” sites (Lindsey and Wicke, 1974). An alternative method is to record voltages with respect to a vertex reference (electrode Cz), which is considered to be a “symmetric” reference with respect to both hemispheres. However since Cz is undoubtedly an electrically active site, its selection as reference results inevitably into low signal-to-noise ratio, especially for the frontal parts of the brain (Hagemann, 2004). Another commonly used montage is the computationally-linked earlobes/mastoids reference, which provides a virtual symmetric reference. However, these sites are not completely inactive either (Hagemann et al., 2001). Another option is the use of the average activity of all recording sites as the reference value. Provided that the electrode placement is dense and it covers the whole of the head, the common average reference could be the most suitable choice (Bertrand et al., 1985).

A method which could overcome the problem of selecting a common reference is the employment of bipolar recordings, which is the measurement of potentials differences between adjacent electrodes. The significant drawbacks of this method are that the bipolar pairs of electrodes can only detect dipoles with certain locations and orientations (Schiff, 2005). Furthermore, they may also detect activity from distant sources and they do not provide definitive information about the polarity of a dipole source generator (Katznelson, 1981).

A different, reference-free approach employs the use of Current Source Density (CSD) derivations (Hjorth, 1975). The aim, in this case, is to indicate scalp areas where electrical current emerges from (i.e. sources) or converges into (i.e. sinks) the scalp. This

is achieved by calculating the surface Laplacian of the instantaneous scalp potential, which is proportional to the radial current flow, which in the case of a simple dipole, is proportional to the dura surface potential (Srinivasan, 2005). A limitation of the CSD method is that, by essentially acting as spatial high-pass filter (Srinivasan et al., 1996), it underestimates the activities of broad dipole layers. In addition, it can only be reliable for the representation of radial sources, which are not located deep in the brain (Pernier et al., 1988).

1.2.1.2. Source localization – The "inverse problem"

The main advantage of EEG over popular imaging techniques, namely functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET), is its excellent temporal resolution, which lies in the sub-millisecond range. High-density EEG allows for real-time recordings of neuronal population dynamics, widely distributed in the brain, allowing thus the study of functional coupling of anatomically separated cortical areas.

However, an inherent problem in EEG is that the recording electrodes are separated from the activated cortical sources by the scalp, the skull and the cerebrospinal fluid (CSF) and in the case of deep cortical sources, by large parts of the cerebral cortex as well. Each of these areas holds a different conductivity value. As electrical currents flow through these areas they get attenuated and most importantly they diverge from the radial direction (Srinivasan, 2005). Moreover, for a given scalp topography there could

potentially be several combinations and configurations of intracranial sources, which could generate the observed voltage pattern.

One approach to the above-mentioned problem (known as the "inverse problem") is the employment of distributed source estimation methods. These methods assume the continuous distribution of electrical sources over the entire brain surface (or volume). A unique solution can be obtained by applying additional constraints, such as the minimum norm constraint, which provides the solution with the minimum intensity (Hämäläinen and Ilmoniemi, 1994). A drawback of the minimum norm method is its inefficiency in representing deep cortical sources, even in the absence of noise (Fuchs et al., 1999). This problem can be addressed by the use of the diagonal matrix weighted minimum norm (WNM) solution (e.g. Gorodnitsky et al., 1995) or the low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994), two methods which compute the three dimensional distribution of the cortical current density.

Another approach is to assume that the activity of a small patch of cortex can be approximated by a single dipole source (sometimes termed as equivalent current dipole (ECD)). A further assumption is that the head can be considered to have a spherical or ellipsoidal shape and it can be divided into three or four concentric spherical or ellipsoidal layers. Each one of them corresponds to head regions, namely the brain, the CSF, the skull and the scalp. Such models can be considered valid if i) the location and orientation of the dipole sources are physiologically plausible and correspond to the scalp topography and ii) the voltage measured on the scalp corresponds to the voltage generated by the dipole source model.

A more sophisticated method for source localization involves the application of beamforming techniques. Unlike ECD methods, beamforming does not require a priori knowledge of the number of sources and it is more immune to noise interference (Halchenko et al., 2005). In beamforming, the activity at each brain voxel is computed by applying a spatial filter, which suppresses interference originating elsewhere in the brain (e.g. Van Veen et al., 1997). A useful attribute of this spatial filtering approach is that it also provides the ability to localize both evoked and induced brain activity (e.g. Praamstra et al., 2006).

1.3. EEG measures in motor control

Sensorimotor processing is typically studied in EEG by exploring the modulation of event related potentials and the frequency-specific changes in the ongoing brain activity.

1.3.1. Event Related Potentials

The majority of EEG research has focused on electrical responses, which are time- and phase-locked to an event, thus termed event related potentials (ERPs). ERPs do not represent activity generated from a single nerve cell; instead, they reflect the summed postsynaptic potentials. Due to their relatively small amplitude (usually in the range of μV) and to the high levels of environmental and biological noise in the EEG signal, ERPs

only become distinguishable after averaging of multiple repetitions. They are typically characterized in terms of polarity, peak latency and scalp topography.

The neurophysiological mechanisms which underlie the generation of the ERPs are still under debate. The classical view supports the existence of an "evoked model", according to which the ERPs are independent from the ongoing cortical rhythms and are simply superimposed over the background oscillatory activity and noise (e.g. Jervis et al., 1983). An alternative and more recent view suggests that the ERPs are generated by phase resetting of the ongoing cortical rhythms without any amplitude modulation (pure phase resetting) (Sayers et al., 1974) or with a parallel increase in amplitude (phase resetting with enhancement) (Başar et al., 1980). However, although increasing evidence supports the existence of a phase resetting mechanism (Hanslmayr et al., 2007), the important role of stimulus-evoked activity in ERPs generation cannot be disregarded (Shah et al., 2004).

A wide variety of ERPs can be elicited by repeated occurrences of cognitive, motor or sensory events. Sensory evoked potentials, which are perhaps the most extensively studied type of ERPs can be elicited by somatic, auditory, visual, odour or taste stimulation. Sensory evoked potentials can be divided into two categories depending on the presentation rate of the driving stimulus: transient evoked potentials and steady-state evoked potentials. Transient evoked potentials are elicited by relatively low stimulus presentation rates (depending of the onset latency of each component). Steady state evoked potentials are sinusoidal signals oscillating at the frequency (presentation rate) of the driving stimulus. The optimal frequency for eliciting steady-state evoked potentials is

modality specific. In the auditory domain it is around 40 Hz (Galambos et al., 1981) whilst in the visual domain it is around 10 Hz for unpatterned and 6 Hz for patterned visual stimuli (Regan, 1982). Steady state somatosensory evoked potentials are optimally elicited in intermediate frequencies, around 21-26 Hz (Snyder, 1992; Tobimatsu et al., 1999).

Another type of ERPs are the movement related potentials, which are not only elicited during action execution, but also during preparation for action. The preparatory movement potentials (the study of which constitutes a big part of the present thesis) are slow rising electrophysiological signals of negative polarity, which occur before self-paced (Bereitschaftspotential or Readiness potential, see Section 1.8.1.) and externally triggered movements (Contingent Negative Variation (CNV), see Section 1.8.2.).

An interesting phenomenon is the decrease in amplitude for of short-latency SEPs (sensorimotor gating) and the increase in amplitude of the long-latency SEPs before and during active or passive movement (e.g. Cheron and Borenstein, 1991; Valeriani et al., 1999; Wasaka et al., 2003; Kida et al., 2006a). The former is believed to result from a centrifugal mechanism whereby efferent motor activity attenuates the ascending somatosensory signals, whereas the later could involve a centripetal mechanism as well, through which afferent somatosensory signals generated by movement enhance the amplitude of stimulus-elicited SEPs (e.g. Jones et al., 1989).

1.3.2. Event related frequency-specific oscillatory changes

Cortical oscillations are rhythmic periodic fluctuations of the brain electrical activity, which originate from frequency-specific, synchronous firing of large neuronal populations, either driven by oscillatory firing patterns of pacemaker cells and/or emerging through the properties of the network architecture (Singer, 1993). The number of synchronously firing neurons is directly related to the amplitude and inversely related to the frequency of the oscillations (Lopes da Silva, 2004).

Depending on their frequency, cortical rhythms have been subdivided into bands. Each frequency band has its own distinctive functional role and cortical topography. The cortical rhythms that are mostly related with motor tasks and constitute an important part of the present thesis reside in the alpha band (7-13 Hz) and the beta band (14-30 Hz). The amplitudes of these rhythms are modulated in response to external (e.g. sensory stimulus) or internal events (e.g. self-initiated action). Typically, an increase in amplitude of alpha or beta oscillations is linked to an "idling" or inactive cortical state, whereas a decrease in amplitude denotes activation or inhibition of the associated cortex (Pfurtscheller and Lopes da Silva, 1999). The modulation of the alpha rhythm is usually observed over parieto-occipital and frontal areas and it is related to alertness, attention and semantic memory processes (Klimesch, 1999). The modulation of the beta rhythm, observed primarily over motor and premotor areas, is associated with motor preparation and execution, observation of movement and motor imagery (Neuper et al., 2006).

In addition, cortical oscillatory activity in the gamma band (30-90 Hz) is often studied in a variety of tasks (including motor tasks) and is regarded as the binding mechanism

among cortical areas, serving selective attention, working memory sensorimotor integration, action preparation and response selection (Womelsdorf and Fries, 2006). However, gamma oscillations were not studied in the present thesis, so they will not be discussed any further.

The quantification of event-related oscillatory changes in a specific frequency band comprises the following steps: i) band-pass filtering of the data, ii) rectifying (Salmelin and Hari, 1994b) or, equivalently, squaring (Pfurtscheller and Lopes da Silva, 1999) of the signal amplitude in order to obtain the temporal spectral evolution (TSE) or the power of the signal, respectively and iii) averaging across trials. The decrease in amplitude within a frequency band is termed Event Related Desynchronization (ERD) (Pfurtscheller and Aranibar, 1977), whereas the increase in amplitude Event Related Synchronization (ERS) (Pfurtscheller, 1992).

1.4. Preparation for Action as a function of uncertainty reduction

Preparation for action involves processes through which memory of past events, salient characteristics of the environment and anticipation of forthcoming events are encoded in such a way as to produce the optimal motor response. This goal can be achieved by reducing the energy costs of the physiological processes required for the performance of an action and/or the formulation of a qualitatively adequate task-specific response.

Central in understanding the function of preparation for action is the concept of uncertainty (for a comprehensive review, see Requin et al., 1991), which can be

described as the inability of an organism to precisely foresee the timing and the physical properties of an external event, as well as the outcome of the required action. The encounter of a novel situation is naturally related to maximum uncertainty, which leads to an entirely reflexive response of unspecified energy requirements. The purpose of action preparation is the reduction of uncertainty, which can be achieved by the regulation of energy expenditure (tonic preparation) and/or by the selection of the parameters of the appropriate response (event phasic preparation) and the estimation of the right moment in time for the performance of the required action (temporal phasic preparation).

1.4.1. Tonic Preparation

Tonic preparation is implemented by restricting the activity of the striate muscles to the minimal amount required for achieving the desired behavioural goals (Requin et al., 1991). Regulation of striate muscle activity has been associated to anticipatory cardiovascular (e.g. Mäntysaari et al., 1988) and pulmonary processes (e.g. Tobin et al., 1986). However, these types of studies fall beyond the scope of the present thesis, so they will not be discussed any further.

1.4.2. Phasic Preparation

Phasic preparation can be categorized into temporal preparation (when to respond) and event preparation (how to respond).

The objective of temporal preparation is to minimize the temporal uncertainty regarding the occurrence of an anticipated event. It was originally believed that it affects late processes related to motor preparation (e.g. Spijkers, 1990; Sanders, 1998), although recent electrophysiological evidence suggests that temporal preparation also enchances the processing speed of early premotoric processes (e.g. Müller-Gethmann et al., 2003; Bausenhart et al., 2006). As illustrated by (Bertelson, 1967) an optimal state of preparation is achieved at a minimum time of 150ms and it cannot be maintained for more than 250ms. Moreover, when a participant is required to produce successive responses, the necessary time to "reprepare" after the completion of one response is estimated to be about 900ms (Alegria, 1974). An interesting question is how a person prepares to respond when facing alternative possible times at which an event is expected to occur. Alegria (1974) proposed a discrete model in which a person simply uses the timing information from his/her previous response and "reprepares" if the event does not occur at the expected time. In contrast, Durup and Requin (1970, in Requin et al., 1981) proposed an alternative model, in which all possible alternatives are prepared in parallel irrespective of the timing of the previous response.

The same question applies to the case of event preparation, when a person has to prepare alternative responses (e.g. left or right hand responses, high or low level of force etc.). Traditional theories suggest that specification of response parameters occurred in a serial way; collection of sensory information leads to representation of the environment, which in conjunction with memories from previous actions, leads to the formation of an action model, which ultimately results to the required response. Recent converging evidence, however, support the view of parallel preparation, according to which

representations of all possible actions are processed in a continuous and mutually inhibiting manner, until the moment where sufficient information is collected, which allows the specification of the appropriate response (e.g. Bastian et al., 2003; Cisek and Kalaska, 2005).

1.5. Internal models in motor control

Various studies have shown that the central nervous system (CNS) constructs internal models of sensorimotor transformation in order to determine the motor commands necessary for the implementation of the appropriate action (Kawato et al., 1987; Jordan, 1995). A type of internal models is the "feedback" models, according to which there is no pre-existing specific motor plan. Instead, the movement parameters are adjusted relative to the ongoing feedback during the performance of the action (e.g. Flanagan et al., 1993). An inherent weakness of these models comes from the fact that the minimum time for sensory feedback to influence a movement is as least 80-100 ms, which is not adequate for controlling rapid movements (Jeannerod, 1988; Paillard, 1996). Such delays, along with the intrinsic "neural noise" of physiological signals (Harris and Wolpert, 1998) render purely feedback models as incomplete.

"Feedforward" models, on the other hand, propose that the motor command and its consequences are predefined before the performance of an actual movement (Wolpert and Miall, 1996). These models suggest that the brain, instead of relying on sensory feedback, utilizes an "efference copy" of the motor command, which is passed into a

feedforward system, which simulates the kinetics and/or the kinematics of the prepared action as well as the behaviour of the external environment. Depending on whether the prediction pertains to the position of the body or the sensory feedback after the movement, forward models can be divided into forward dynamic and forward sensory models (Witney et al., 2004).

Despite the self-evident advantages of feedforward control especially in the control of rapid movements, several studies have shown that the most likely internal model is a hybrid one, which represents a trade-off between purely feedback and feedforward models (Hoff and Arbib, 1993; Wolpert et al., 1995; Gribble and Ostry, 1999). The hybrid model supports the existence of a pre-movement broadly-specified forward model (Blakemore et al., 1998; Gribble and Ostry, 1999; Desmurget et al., 1999; Bhushan and Shadmehr, 1999), which operates under the constant supervision and updating of internal feedback control (Desmurget and Grafton, 2000).

1.6. Studying CNS function at the periphery

Indirect studies of the central processes that govern motor control can be made by studying their peripheral effects. This can be achieved by studying the kinetics and kinematics of a movement, the time of initiation (i.e. reaction times) and the activity of the relevant muscles.

1.6.1. Biomechanical and Chronometric studies in anticipatory motor control

Several biomechanical studies have investigated anticipatory/predictive motor control, shedding light on the operation of internal predictive models. For example, when handling objects, the grip force that a person uses, rises prior to lifting, moving the object or resisting to an anticipated external load (Johansson and Westling, 1984a, 1988b; Flanagan and Wing, 1993, 1995, 1997). Studies on prehensile movements have demonstrated that various kinetic (finger positioning, maximum grip aperture etc.) and kinematic (movement time, peak velocity etc.) parameters are pre-adjusted according to target properties before handling the target (Jakobson and Goodale, 1991; Carnahan and McFadyen, 1996; Gentilucci et al., 1996). Anticipatory postural adjustments have also been measured before self-initiated or externally-triggered postural perturbations, by measuring accelerations of the trunk and the lower limb and modulations of ground reaction forces (Bouisset and Zattara, 1987; Wing et al., 1997; Jacobs and Horak, 2007).

Chronometric methods make inferences about the time course of information processing (Coles, 1989), relying on the notion that a person responds faster to an external event, when he/she has prior knowledge about the timing of the event and/or the movement parameters of the appropriate response. Therefore, the measurement of reaction times could provide information about a person's state of motor preparation. Full or partial advance specification of certain features of the response (selection of finger, movement direction etc.) results in shortening of reaction times (e.g. Miller, 1982; Lepine et al., 1989). The typical paradigm, usually called movement-precuing paradigm (Goodman and Kelso, 1980; Rosenbaum, 1980), for studying changes in reaction times in

event preparation, consists of a choice-reaction task where an informative cue stimulus provides full or partial information about the upcoming response, followed by an imperative stimulus which prompts a person to react. Although it has been the standard paradigm in the last three decades for studying movement preparation, there is still a possibility that the information carried by the cue stimulus simply reduces the number of stimulus-response alternatives without any advance specification of movement parameters (Goodman and Kelso, 1980). Modulation of reaction times has also been studied in tasks where temporal preparation was investigated by manipulating the duration of the time interval between the informative and the imperative stimulus (Niemi and Näätänen, 1981; Sollers III and Hackley, 1997; Los and van den Heuvel, 2001). Shortening of reaction times have not only been observed in simple reaction tasks (i.e. where the response is the same in all trials) (Woodrow, 1914, in Requin et al., 1991) but in choice-reaction tasks as well (Bertelson and Boons, 1960), indicating that temporal preparation can occur independently of event (un)certainty.

1.6.2. Electromyography

Preparatory muscle activity prior to performance of an action can be directly assessed by means of electromyography (EMG). Activity in muscles (agonists as well as antagonists) relevant to a response increases in preparatory fashion in a variety of tasks that may involve muscles of the upper and lower extremities as well as the trunk (Brunia and Vingerhoets, 1980; Lee, 1980; Haagh and Brunia, 1985; Johansson and Westling, 1988a; Johansson and Westling, 1988b). It should be noted though that the correlation between

increased preparatory muscle activity and reaction times is rather weak (Sanders, 1983). Pre-movement muscle activity does not probably reflect processes related to specific motor preparation, but it is rather a sign of a state of general preparation before movement execution (Haagh and Brunia, 1985).

EMG provides also the ability to study another aspect of anticipatory motor control, which is the modulation of reflex responses induced in muscles involved in a task when a person faces an external load/perturbation. Reflexes, as measured by EMG, can be divided in two categories: the spinally-mediated short-latency reflexes (SLRs) and the long-latency reflexes (LLRs) whose generation probably involves a supraspinal loop (Cheney and Fetz, 1984; Capaday et al., 1991; Johansson et al., 1994; Macefield et al., 1996b; MacKinnon et al., 2000). Both SLRs and LLRs are reduced in amplitude when the external perturbation is of predictable nature, as a result of anticipatory pre-movement muscular adjustments (Johansson and Westling, 1988a; Goodin et al., 1990; Leinonen et al., 2002). The LLR modulation in particular (discussed in more details in Chapter 3), due to its cerebral origins is considered as evidence for the existence of a feedforward internal model, which operates during involuntary/reflexive motor control (Kurtzer et al., 2008).

1.7. Neural control of movement

The self-evident weakness of all the methods described in the previous section, is that they do not examine the central processes at the cortical or subcortical level; instead they measure their peripheral effects. The technological advances of the last decades have

made possible the detailed anatomical representation of the whole brain, by making use of the principle of the Nuclear Magnetic Resonance (NMR) of hydrogen atoms, which led to the development of the ubiquitous Magnetic Resonance Imaging (MRI) method. A major step in the study of neural processes was the introduction of functional MRI (fMRI), which produces remarkably accurate static images of all the brain areas that are activated during a task. Equivalent results can be obtained using the Positron Emission Tomography (PET) method with the expense of injecting a comparatively large amount of radioactive radiopharmaceuticals into a person. However, despite the excellent spatial localization offered by these two methods, the temporal resolution of the produced data is extremely poor. The answer to this problem (see Section 1.1) is provided by the employment of Electroencephalography (EEG) and the equally accurate however more expensive, Magnetoencephalography (MEG) method. The comparison of the findings of all these methods in similar experimental designs could potentially produce spatially as well as temporally accurate functional representations of brain processes in various tasks, including motor control, which is the topic of the present thesis.

In the following section, we will present the brain areas which are mostly associated to motor control, as demonstrated by a series of experiments using the afore-mentioned neurophysiological methods.

1.7.1. Brain areas involved in motor control

The preparation and execution even of a simple movement involves the activation of multiple cortical and subcortical areas. The cortical areas directly engaged in motor control are the primary motor, the premotor and the posterior parietal cortex, whereas areas receiving sensory input from the periphery (e.g. primary somatosensory cortex, visual cortex etc.) and areas with cognitive functions (e.g. prefrontal cortex) play an important indirect role in the formation, evaluation and adjustment of a motor plan. In addition, reciprocal connections between the cerebral cortex and deep brain areas, such as the cerebellum and the basal ganglia, are necessary in planning, initiation and coordination of complex motor activities (Patestas and Gartner, 2006; Bear et al., 2007).

The basal ganglia and the cerebellum are thought to have a complementary role. The basal ganglia operate as context encoders responsible in planning and gating of inhibitory and excitatory signals, while the cerebellum is involved in preparation, coordination and execution of a movement. The cerebral cortex has a repository function receiving input from the periphery, computing and sharing complex information with the basal ganglia and the cerebellum, and an executive function in producing the appropriate action (Patestas and Gartner, 2006; Bear et al., 2007).

1.7.1.1. The Cerebellum

The cerebellum resides in the inferior posterior part of brain below the occipital lobes. It consist of a core of white matter, surrounded by three layers of gray matter (the cortex),

which consists of an outmost molecular layer, an intermediate Purkinje cell layer and an innermost granular layer (Andersen et al., 1992). The importance of the cerebellum in a wide range of neuronal activities is reflected in its extreme density; the number of cerebellar cells is more than four times higher than the number of cells in the cerebral cortex (Pakkenberg et al., 1989), whereas the number of granule cells exceeds the total number of neurons in the whole human body (Andersen et al., 1992).

The pivotal role of the cerebellum in the control of complex movements has been demonstrated as early as 1917 (Holmes, 1917). It should be noted that the cerebellum is also involved in the control of non-motor activities (e.g. Bellebaum and Daum, 2007; Ito, 2008). However, this functional aspect of the cerebellum is beyond the focus of the present essay. In motor control, the cerebellum integrates sensorimotor information received from the cerebral cortex and the periphery in order to plan, modify and coordinate movements (Patestas and Gartner, 2006). In addition, it has been associated to motor learning (Marr, 1969; Raymond et al., 1996) and also to the processing of temporal information, playing the role of general-purpose biological clock (Braitenberg, 1967; Ivry, 1996). However, these seemingly distinctive functional roles are not mutually exclusive; as proposed by Ohyama et al. (2003), the cerebellum may reflect feedforward processing, which leads to the coordinated execution of movements via temporally specific motor learning processes (Mauk et al., 2000).

1.7.1.2. The Basal Ganglia

Another subcortical structure embedded deep in the white matter of the brain, associated with motor control, is a collection of large brain cells, collectively known as the basal ganglia. The basal ganglia, which are in fact nuclei, consist of the striatum (caudate nucleus, putamen and nucleus accumbens), the dorsal (globus pallidus) and the ventral pallidum, the subthalamic nucleus and the substantia nigra (Patestas and Gartner, 2006; Bear et al., 2007). With regard to their functional role, the striatum and the subthalamic nucleus are characterized as input nuclei, the substantia nigra (pars reticulate) and the internal/medial globus pallidus as output nuclei, whereas the external/lateral globus pallidus and the ventral pallidum (Maurice et al., 1997) are regarded as intrinsic nuclei which have local interconnections with other nuclei of the basal ganglia (Patestas and Gartner, 2006).

The basal ganglia are involved in the preparation for execution of self-initiated (Monchi et al., 2006) and externally triggered movement and in the automatic execution of learned motor plan (Afif and Bergman, 1998). They are believed to subserve the selective initiation of a movement by facilitating wanted and inhibiting unwanted aspects of the motor action (Mink, 1996). The basal ganglia connect via the thalamus to the cerebral cortex in a parallel manner (Alexander and Crutcher, 1990), providing internal cues for the smooth running of a movement (Haas, 2005). Dysfunction of the basal ganglia leads to a number of movement disorders, characterized either of hyperkinesia (e.g. Huntington's disease) or hypokinesia (Parkinson's disease) (Afif and Bergman, 1998).

1.7.1.3. Posterior Parietal Cortex (PPC)

The posterior parietal cortex is situated between the frontal and occipital lobes and above the temporal lobe and it is anatomically divided by the postcentral sulcus into the superior and the inferior parietal lobule (SPL and IPL). The SPL (Brodmann's areas 5 and 7) is typically considered to be an association area involved in somatosensory function and behavioural integration with the surrounding environment. The IPL (Brodmann's areas 39 and 40) is subdivided into the angular gyrus which receives visual input and the supramarginal gyrus, which integrates visual, auditory and somatosensory information (Patestas and Gartner, 2006). The major functional role of the posterior parietal cortex is the representation of space by integrating inputs from various sensory modalities (i.e. vision, audition, somatosensation and vestibular sensation) as well as efference copies of motor commands generated in the frontal lobes (Andersen et al., 1997). Multiple representations of space coexist in a number PPC areas. The ventral intraparietal area (VIP) represents perioral space, the medial intraparietal area (MIP) immediate extrapersonal space, the lateral intraparietal area (LIP) more distant space explored with eye-movements, whereas the anterior intraparietal area (AIP) is involved in grasp-related representation of space (Colby and Goldberg, 1999). This important function of the PPC does not only serve the orientation of attention to salient environmental stimuli, but also plays a central role in movement selection and intention (Snyder et al., 2000). In addition, recent studies have identified a PPC region, which gets activated when a primate prepares a reaching movement even with-no spatial information (see, "the parietal reach region (PRR)", Batista and Andersen, 2001; Nishimura et al., 2007; Cui and Andersen, 2007). The involvement of the PPC in motor preparation is also reflected in the fact that several

studies have shown that it is an essential contributor in the formation of predictive internal models, which are engaged in conscious control of voluntary actions (Blakemore and Sirigu, 2003; Sirigu et al., 2004).

1.7.1.4. Premotor Cortex (PMC)

The premotor cortex (Brodmann's area 6) residing directly anterior to the primary motor areas was first identified by Cambell (1905, in Wise, 1985), who initially called it the "intermediate precentral cortex". Its medial part, termed the supplementary motor area (SMA or MII) is associated with temporal organization and sequential performance of self-generated movements, coordination of bilateral movements and retrieval of motor memory (Afif and Bergman, 1998; Bear et al., 2007). The SMA can be functionally divided into the preSMA (rostral SMA), which receives input from the cerebellum, prefrontal and cingulated areas and the SMA proper (caudal SMA), which receives input from the basal ganglia and projects its output to the primary motor cortex and the spinal cord (Afif and Bergman, 1998). The preSMA is mostly involved in motor imagination, selection and control, whereas the SMA proper in motor execution (Luppino et al., 1993; Stephan et al., 1995; Deiber et al., 1996; Lee et al., 1999; Schubotz and von Cramon, 2001a).

Activation of the lateral PMC (for which the term "premotor cortex" is often reserved) has been associated to sensory driven voluntary movements, motor preparation and programming, reaching, obeying a spoken command, object identification by

manipulation, limb stabilization through control of axial and proximal musculature, vasomotor regulation and selective attention (Rizzolatti et al., 1983; Wise, 1985; Afif and Bergmann, 1998). The (lateral) PMC can be divided into the dorsal premotor cortex (PMd), which receives input from the superior parietal lobule and the dorsal area of the dorsolateral prefrontal cortex and the ventral premotor cortex (PMv), which receives input from the inferior parietal lobule and the ventral area of the dorsolateral prefrontal cortex (Johnson et al., 1996; Matelli et al., 1998; Hoshi, 2006). The functional role of the PMv seems to be more important in direct motor control, matching sensory signals to motor output and observed actions to self-movements (see, "the mirror-neuron system", e.g. Rizzolatti and Craighero, 2004). By contrast, the PMd is an integral part of conditional motor behaviour (i.e. the arbitrary mapping of sensory information onto specific actions, Petrides, 1986; Mitz et al., 1991; Toni et al., 2001) and in general of indirect motor control, receiving multiple motor-related sensory inputs, integrating movement parameters (e.g. movement direction and amplitude) and constructing a motor plan for the required action (Hoshi and Tanji, 2007).

1.7.1.5. Fronto-parietal networks

The frontal and parietal areas are interconnected in various ways as to form functional networks, which mediate the sensorimotor transformations for the control of attentional shifts, preparation of limb movements and representations of other persons' actions. Interestingly, bidirectional connections exist between each parietal area and

predominantly a single premotor area (Matelli and Luppino, 2001); for example MIP is reciprocally interconnected to PMd, AIP to PMv, LIP to FEF etc..

A concept relevant to the present dissertation is that spatial attention and saccade programming are mediated by a shared fronto-parietal network (see, "the premotor theory of attention", Rizzolatti et al., 1987). Later studies clearly demonstrated that this is also the case in the programming of unimanual responses (e.g. Eimer et al., 2005; Praamstra et al., 2005; Gherri et al., 2007). The temporal order in which the frontal and the parietal areas get activated are still a matter of debate; a number of studies suggest that activation of frontal cortices precedes parietal activation e.g. Corbetta and Shulman, 2002; Grent-'T-Jong and Woldorff, 2007), while others studies point towards the opposite direction (e.g. Yamaguchi et al., 1994; Hopf and Mangun, 2000). However, as Cisek (2007) proposed, the sequence of fronto-parietal activation may depend on task characteristics; for example, if the decision for a response depends on the sensory features, parietal activation would precede the frontal one.

1.7.1.6. The Primary Motor Cortex (MI)

The primary motor cortex (MI) (Brodmann's area 4) is located in the dorsal part of the precentral gyrus of the frontal lobe. Each hemisphere controls the contralateral side of the body and it is somatotopically organized as an upside-down homunculus (Latin: little person), in the sense that the representation area of the toes resides in the superior aspect of MI, while those of the tongue, lips and larynx in the inferior aspect of MI. The cortical

areas dedicated to the control of an action are proportional to its complexity. For example, half of the MI is related to hand and tongue movements, highlighting the importance of speech and manual dexterity in humans (Patestas and Gartner, 2006; Bear et al., 2007).

The functional role of the primary motor cortex is considered to be the specification of movement parameters and the control of execution of voluntary and involuntary (MacKinnon et al., 2000) motor activities (Bear et al., 2007). Single-cells studies have shown MI cells encode the direction and the magnitude of static and dynamic exerted force (Evarts, 1968; Georgopoulos et al., 1992; Maier et al., 1993; Ashe, 1997; Boline and Ashe, 2005), as well as action kinematics, such as movement direction, (Georgopoulos et al., 1982) velocity (Humphrey et al., 1970), distance (Fu et al., 1993) and target position (Fu et al., 1995). In addition to movement planning and execution, the MI is active during motor imagery (Beisteiner et al., 1995; Porro et al., 1996; Szameitat et al., 2007) and also before and during action observation (Hari et al., 1998; Kilner et al., 2004; Kilner and Frith, 2007; Tkach et al., 2007; Koelewijn et al., 2008), which points towards a role of MI in the formation of motor memory and motor learning (Stefan et al., 2005, 2008).

1.8. Event Related Potentials (ERPs) during preparation for action

Several ERPs have been utilized in order to shed light on the neural mechanisms which control the anticipation/preparation and the execution of an action. The ones most relevant to the present thesis are discussed in this section.

1.8.1. The Bereitschaftspotential (BP) – Readiness Potential (RP)

The Bereitschaftspotential or Readiness Potential is a cortical potential of negative polarity, which develops prior to self-initiated movements. Originally reported by Kornhuber and Deecke (1965), it is typically considered to be an index of motor preparatory activity. It is divided in two major subcomponents, an early one often referred to as BP1, early BP and negative slope 1 (NS1), starting 1.5-2 sec before movement onset and a later one referred to as BP, BP2, late BP, NS, NS2 and motor cortex potential, which starts ~500 ms before movement onset and it is characterized by a steeper gradient (Jahanshahi and Hallett, 2003). Two additional subcomponents were identified by Deecke et al. (1969), a positive deflection ~100 ms before movement onset, referred to as premotion positivity (PMP) and a negative one ~50-60 ms before movement onset referred as peak BP, peak NS or motor potential (MP) being stronger over motor areas contralateral to the acting hand and directly related to EMG onset (Shibasaki et al., 1980).

The generation of the Readiness potential primarily involves an extended cerebello-dentato-thalamocortical (CTC) network, although basal ganglia activation may

contribute to a smaller degree (Ikeda et al., 1997; Purzner et al., 2007). The role of cerebellar contribution in the generation of the Readiness potential has been emphasized by lesion studies, where it was shown that unilateral cerebellar lesions suppressed the Readiness potential in the motor cortex contralateral to the side of the lesion (Shibasaki et al., 1978, 1986; Sasaki et al., 1979; Gerloff et al., 1996). In terms of cortical structures, the primary motor cortex (MI) and the supplementary motor area (SMA) are strongly involved in the control of the Readiness potential. Cingulate motor and premotor areas contribute to a lesser degree during the early and later stages of the BP, respectively (Colebatch, 2007). Intracranial recordings have demonstrated that both the early and the late BP originate from the SMA and the MI, while the peak BP is associated only with MI activation (Neshige et al., 1988; Ikeda et al., 1992). There is, however, a disagreement regarding the timing of SMA and MI activations. A number of studies have suggested that the SMA and the MI contribute to the BP in a parallel manner (e.g. Ikeda et al., 1992; Praamstra et al., 1996b), while other studies have pointed towards sequential activation of these brain areas (e.g. Deecke, 1987; Cui et al., 2000b). According to the latter view, the SMA is the earlier and main generator of the early BP, while the MI contributes primarily in the late BP (cf. Shibasaki and Hallett, 2006).

1.8.2. Contingent Negative Variation (CNV)

The Contingent Negative Variation (CNV) (Walter et al., 1964) is a cortical electrophysiological signal of negative polarity, which develops progressively during the time interval between a warning stimulus and a subsequent imperative stimulus, which

prompts the participant for a somatic or a noetic response. The CNV is a long latency, slow brain potential, which consists of two subcomponents, an early wave recorded over frontocentral areas and a late wave maximal over centroparietal areas (Rohrbaugh et al., 1976). These two components usually overlap in short interstimulus intervals and become distinguishable when the interstimulus interval is longer than 3 seconds (Rosahl and Knight, 1995).

The early CNV is believed to reflect orienting processes related to the information conveyed by the warning stimulus (Loveless and Sanford, 1974), whereas the late CNV has been related to cognitive and motor anticipatory processes prior to the expected imperative stimulus (cf. Leuthold et al., 2004). The late CNV was associated (Rohrbaugh and Gaillard, 1983) to the Bereitschaftspotential (Kornhuber and Deecke, 1965), which develops before internally-paced movements. However, despite the similarity in waveforms and the well-accepted motoric contribution to the generation of the late CNV wave, this suggestion has been dismissed by more recent studies, on the basis of stimulus-anticipatory processes only present in the case of the CNV and the dissimilar activation of subcortical structures in the generation of the two components (Van Boxtel and Brunia, 1994a; Ikeda et al., 1997; Brunia, 1999; Purzner et al., 2007).

Numerous electrophysiological, imaging and animal studies have reported ramp-like activation patterns from various cortical and subcortical brain areas, indicating that the CNV is most likely generated by an extended thalamo-cortical-striatal network (Komura et al., 2001; Macar and Vidal, 2003; Nagai et al., 2004; Durstewitz, 2004; Pfeuty et al., 2005; Purzner et al., 2007; Fan et al., 2007). The supplementary motor area

(SMA) and anterior cingulate cortex (ACC) are strongly involved in the generation of the early component of the CNV (Gómez et al., 2001; Cui et al., 2000a; Nagai et al., 2004). The generation of the late component of the CNV is associated with various cortical areas, such as ACC (mostly the dorsal part, see Nagai et al., 2004), SMA, primary sensorimotor, premotor, prefrontal, temporal, occipital and parietal areas (Gómez et al., 2001; Gemba et al., 1990; Rosahl and Knight, 1995; Lamarche et al., 1995; Hamano et al., 1997; Yazawa et al., 1997; Cui et al., 2000a; Verleger et al., 2000b; Gómez et al., 2004a; Bender et al., 2005; Gómez et al., 2007). Nagai et al. (2004) in a combined EEG-fMRI study demonstrated the involvement of subcortical structures, namely the insula, the basal ganglia and the thalamus, in CNV-related activity. The authors suggested that the thalamic activity indirectly contributes to the CNV by acting as a "secondary regulator of cortical anticipatory activity". Studies with Parkinsonian patients (i.e. characterized by dysfunction of the basal ganglia), showed that the CNV amplitude is significantly reduced compared to healthy persons (Praamstra et al., 1996a; Ikeda et al., 1997). The strong involvement of the basal ganglia in CNV generation argues in favour of the dissociation between the late CNV and the Bereitschaftspotential (Ikeda et al., 1997; Purzner et al., 2007).

The amount of information conveyed by the warning stimulus is an important factor for the build-up of the CNV wave (Mackay and Bonnet, 1990). In this study, the CNV amplitude was higher when full information was provided by the warning stimulus regarding the direction (flexion or extension) or the response force (weak or strong) of the forthcoming movement, compared to a non-informative warning stimulus. Interestingly, in the case of partial information, the CNV amplitude reached intermediate

values. Similar results were reported by Vidal et al. (1995) where the warning stimulus was either informative or non informative about the response duration. These findings were extended by Ulrich et al. (1998), where the warning stimulus specified one, two or three movement parameters (hand, direction and force) producing analogous results to the the afore-mentioned studies.

It should be noted, however, that the opposite effect (i.e. smaller CNV amplitude when full information was provided by the warning stimulus compared to partial information) has also been reported in series of studies (Van Boxtel et al., 1993; Van Boxtel and Brunia, 1994a, b), a discrepancy that could be attributed (Ulrich et al., 1998; Leuthold et al., 2004) to methodological differences between the studies. In addition, Ulrich et al. (1998) argued that the divergent results were possibly caused by the long interstimulus interval adopted by Van Boxtel et al., (1993) and Van Boxtel and Brunia (1994a, b). This strategy could have led to a decrease of motor preparation, which is known to be weaker for long foreperiod intervals (Niemi and Näätänen, 1981). Consequently, the increase of the late CNV in Van Boxtel et al.'s experiments most likely resulted from processes related to the anticipation of the imperative stimulus. In addition, in Van Boxtel et al.'s studies, the participants had to respond very fast, which probably led to high levels of arousal, consequently to high CNV amplitudes (Vidal et al., 1995). In an earlier study Ruchkin et al. (1986) showed that increased levels of uncertainty in the sensory domain lead to increased late CNV amplitudes. Taken all the above-mentioned studies into account, it is reasonable to assume that preparation is organized in a different manner in the motor and the sensory domain (Brunia, 2003).

The properties of the CNV are of particular interest when it comes to the study of temporal processing. Ruchkin et al. (1977) demonstrated in an early study where subjects had to reproduce a time interval, that the amplitude and latency of the CNV peak correlate with the duration of the reproduced interval. Similarly, the CNV peak amplitude and latency correlate with the perceived duration of an interval, when it is compared to a memorized standard (Macar et al., 1999). The CNV peaks right after the end of a memorized standard interval and starts to decline afterwards (Macar and Vidal, 2003; Pfeuty et al., 2003). Remarkably, the slope of the CNV varies inversely with the memorized interval duration; it is adjusted in such a way as to reach the same amplitude at peak latency (Pfeuty et al., 2005). Corresponding temporal properties have been recorded from neuronal subpopulations located in frontal (Niki and Watanabe, 1979; Akkal et al., 2004), parietal (Leon and Shadlen, 2003) and thalamic (Komura et al., 2001) areas. The time-course of such neuronal activity fits with the "climbing neuronal activity" model (Komura et al., 2001; Durstewitz, 2003, 2004; Reutimann et al., 2004), which proposes the existence of neurons whose slope of activity is inversely related to the duration of the encoded interval. This property is also compatible with models of temporal processing which rely on the presence of a pacemaker – accumulator mechanism. These models postulate that time is represented in the brain in the form of pulses, which are regularly emitted by a pacemaker and then transmitted and temporally stored to an accumulator (e.g. Church, 1984). It has been proposed that it is not the number of pulses, but rather the pulse accumulation rate which encodes the duration of time intervals. Similar to the increase of the climbing neuronal activity slope, the

accumulation rate becomes faster in the representation of longer time intervals (cf. Pfeuty et al., 2005)

1.8.3 Lateralized Readiness Potential (LRP)

The Bereitschaftspotential (readiness potential, BP) and the Contingent Negative Variation (CNV) are two slow-brain potentials evoked before self-paced and externally cued movements, respectively. The BP and the late CNV (see previous two sections) represent dynamic changes in premotoric and motoric activity during anticipation and/or preparation of movement. Both potentials initially exhibit a symmetrical bilateral activation, which gradually becomes lateralized prior to response onset, showing higher (negative) amplitude over the hemisphere contralateral to the responding hand. This asymmetry is higher over the motor cortex, indicating the point in time where the selection of the response side has been determined (Kutas and Donchin, 1980).

An electrophysiological marker of this asymmetry is the lateralized readiness potential (LRP) (cf. Coles, 1989) the onset of which denotes the onset of selective response activation, whilst its peak corresponds to the time of the executed response. The LRP was originally introduced in 1988 by two different research groups working in parallel (Gratton et al., 1988; De Jong et al., 1988). De Jong et al. (1988) computed the LRP (to which they gave the label "corrected motor asymmetry") by means of the "double subtraction method". At first, activity recorded over the right motor cortex (e.g. recording site: C3') was subtracted from activity recorded over the left motor cortex (e.g.

recording site: C4'). This procedure was performed separately for left and right hand responses. Finally, the difference waveforms for right hand responses were subtracted from the difference waveforms for left hand responses, thus creating the LRP waveforms (Formula 1).

$$\mathrm{LRP}(t) = (\mathrm{C3'}(t) - \mathrm{C4'}(t))_{\text{left hand}} - (\mathrm{C3'}(t) - \mathrm{C4'}(t))_{\text{right hand}} \quad (1)$$

Coles (1989) employed a slightly different procedure for the computation of the LRP, named the "averaging method". It this method, activity recorded over the motor cortex ipsilateral to the response side was subtracted from activity recorded over the motor cortex contralateral to the response side. This procedure was performed separately for left and right hand responses. The LRP results from averaging the two difference waveforms (Formula 2).

$$\mathrm{LRP}(t) = \frac{(C'4(t) - C'3(t))_{lefthand} + (C3'(t) - C4'(t))_{righthand}}{2} \quad (2)$$

A difference between the "double subtraction method" and the "averaging method" is that in the former case correct responses result in positive LRP values, whereas in the later case to negative ones. Additionally, the LRP amplitude computed using the "averaging method" is half the size of the LRP amplitude computed using the "double subtraction method".

The view that the LRP is an index of motor activation is in agreement with findings from several electrophysiological, neuromagnetic and intracranial animal studies (Riehle and Requin, 1989; Gemba and Sasaki, 1990; Kristeva et al., 1991; Ikeda et al.,

1992; Praamstra et al., 1996b), which reported lateralized activity in the primary motor cortex (MI) and the supplementary motor area (SMA), which was stronger contralateral to the side of the prepared response. The important contribution of MI to the LRP has been substantiated by the seemingly paradoxical increased ipsilateral negativity of the BP, which precedes foot movements (Brunia, 1980; Boschert and Deecke, 1986; Jentzsch and Leuthold, 2002). However, due the somatotopical representation of the foot within the longitudinal fissure, a current dipole source located in the contralateral primary motor cortex projects its activity to the ipsilateral hemisphere (Brunia and Van den Bosch, 1984; Böcker et al., 1994). The finding that the LRP displays opposite polarity for foot compared to hand movements (Osman and Moore, 1993; Carrillo-de-la-Peña et al., 2006) supports the view that it is primarily generated in the MI. Importantly, the somatotopic organization of other areas which may contribute to the LRP, namely the premotor area, supplementary motor area, the frontal eye fields and the cerebellum do not produce such "paradoxical" lateralization, so their contribution to the LRP, if any, should be minimal (Miller and Hackley, 1992).

Certain parameters such as complexity (Hackley and Miller, 1995), speed and accuracy (Osman et al., 2000) of movement modulate the LRP. On the contrary, the force level and rate of force development ((Sommer et al., 1994), but for the opposite view see Ray et al., 2000)) and the direction (e.g. finger flexion vs. extension) of movement (Deecke et al., 1980) do not seem to have a large effect on it. Remarkably, in tasks where different stimulus attributes dictate the response side and whether to respond or not, the LRP can be detected even in the absence of an overt response (no-go trials) (Miller and Hackley, 1992; Osman et al., 1992), which makes the LRP a useful tool in studies of

motor imagery (Carrillo-de-la-Peña et al., 2006) and motor observation (Van Schie et al., 2004).

LRP waveforms can be derived with respect either to stimulus onset or response onset. In the former case, the time interval between stimulus and LRP onsets (S-LRP interval) is considered a measure of premotoric processes that occur prior to response selection. On the other hand, in response-locked data, the time interval between LRP and response onsets (LRP-R interval) reflects processes related to the central organization of the response and to motor execution (cf. Eimer, 1998; Masaki et al., 2004).

A large number of studies have explored the functional significance of the LRP, by examining whether the LRP amplitude and/or onset latency are affected by early (premotoric) or late (motoric) processes. Specifically, parameters related to premotoric processes, such as stimulus intensity (Miller et al., 1999; Jaśkowski et al., 2007), stimulus quality (Smulders et al., 1995) and response validity (Leuthold, 2003) have an effect only on the S-LRP interval. Interestingly, it has been demonstrated that temporal preparation, contrary to the prevailing notion that it affects the duration of motoric processes, increases the duration solely of the S-LRP interval, thus facilitating early premotoric processes (Müller-Gethmann et al., 2003; Hackley et al., 2007). On the other hand, parameters that are associated with motoric processes, such as response complexity (Hackley and Miller, 1995; Smulders et al., 1995), speed-accuracy trade-off (Osman et al., 2000; Van der Lubbe et al., 2001), partial or full advance information (Leuthold et al., 1996) and the number of alternative responses of the selected hand (Miller and Ulrich, 1998) modulate the duration of the LRP-R interval.

An interesting issue, which rather surprisingly has been addressed by a limited number of studies, is the determination of the locus of the LRP onset within the cognitive system. For choice-reaction tasks, the preparatory processes can be divided into perceptual and response-related processes (although they do not necessarily evolve in a serial manner, see Cisek, 2007). The latter ones consist of at least three stages: response selection, response programming and motor adjustment (cf. Masaki et al., 2004). Smulders et al. (1995) argued that the LRP originates either during the response selection stage or between response selection and programming. Miller and Ulrich (1998) reported that the LRP onset, although it follows hand selection, it occurs before the selection of the responding finger. Masaki et al. (2004) attempted to resolve this issue by manipulating parameters, which exclusively affect either the response selection stage (response compatibility) or the response programming stage (movement velocity). Their results showed clear effects of response compatibility and movement velocity exclusively on the S-LRP and the LRP-R intervals respectively, which led the authors to argue that the LRP onset occurs after the completion of response selection and at the start of the response programming process.

1.8.4. Attention Directing Lateralized Evoked Potentials (EDAN, ADAN and LDAP)

A sequence of lateralized components (Figure 1.1), other than the above mentioned LRP, is elicited during the interval between attentional/informative cues, which instruct the participants to direct their attention to the left or the right hemispace and/or to prepare a left or a right handed response and subsequent imperative stimuli, which prompt the

participants to act. The first, in a temporal order, lateralized component was observed in the form of an enhanced negativity over posterior electrode sites, contralateral to the side of the attentional shift, termed early directing attention negativity (EDAN). This is followed by an enhanced negativity recorded over frontal sites contralateral to the side of the attentional shift, termed anterior directing attention negativity (ADAN). Temporally overlapping with the later part of the ADAN but of greater duration, an enhanced positivity has also been observed over posterior sites, termed late directing attention positivity (LDAP). All these components are derived by either using the "double subtraction method", by computing the difference between contralateral and ipsilateral waveforms or by subtracting ERP waveforms elicited by left and right pointing stimuli.

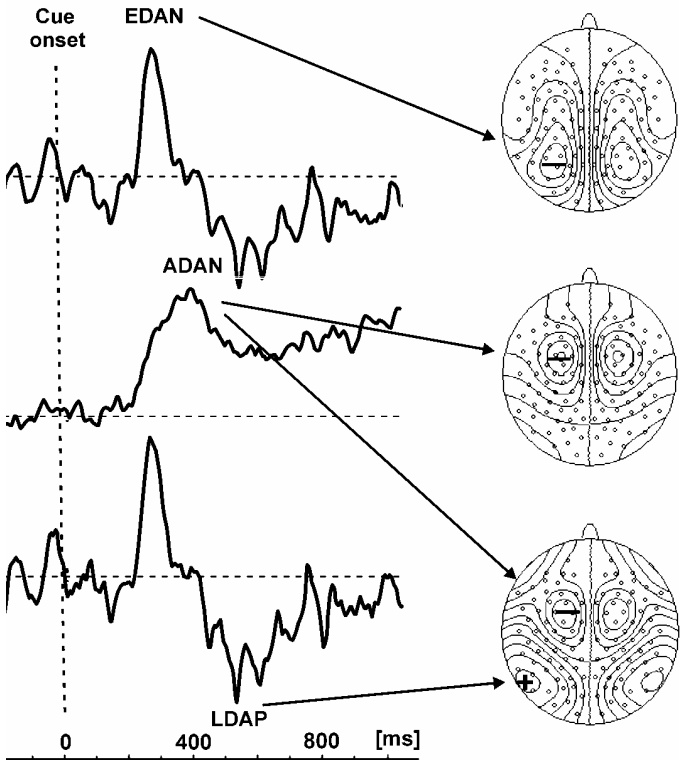

Figure 1.1: Typical waveforms of the EDAN, ADAN and LDAP components and their respective topographies, created from data obtained in the experiment discussed in Chapter 5.

1.8.4.1. Early Directing Attention Negativity (EDAN)

The early attention directing negativity (EDAN) was first observed by Harter et al. (1989) in a visuo-spatial orienting task. The authors reported a posterior negativity stronger over contralateral sites, 200 to 400 ms after the directional cue, which they related to attention directing processes. The EDAN has been reproduced in studies requiring shifts of visuo-spatial attention (Yamaguchi et al., 1994, 1995; Hopf and Mangun, 2000; Nobre et al., 2000) and it has also been interpreted as a mark of initiating the process of directing attention towards the spatial locus indicated by an assymetrical directional (arrow shaped) cue. Since no EDAN is elicited by auditory or tactile cues (Eimer and van Velzen, 2002; Eimer et al., 2002), it is believed that the EDAN is exclusively mediated by visuo-spatial attentional mechanisms.

A possible confound in all the afore-mentioned studies, was that the EDAN was elicited by assymetrical directional cues. Also, in terms of topography and latency, the EDAN was usually similar to the N2pc component (Luck and Hillyard, 1994), which has been observed in visual search tasks. The N2pc component is considered to reflect spatial filtering processes, either inhibition of irrelevant features (Luck and Hillyard, 1994) or facilitation of relevant features (Eimer, 1996). Van Velzen and Eimer (2003) stated that the EDAN is probably a "disguised" N2pc component, elicited by simply orienting attention towards the task-relevant part of the directing cue. Jongen et al. (2007) argued that the EDAN does not reflect sensory processes induced by stimulus asymmetry nor attention orienting. Instead, they suggested that the EDAN is related to the "encoding of directional information from arrow cues". They also argued that the EDAN possibly

overlaps spatially and temporally with the early phase of the LDAP, which due to their opposite polarities, leads to amplitude attenuation or even cancellation. Common origins for the EDAN and LDAP have also been reported by Van der Lubbe et al. (2006), who tentatively placed their generators in the ventral intraparietal sulcus (vIPS).

1.8.4.2. Anterior Directing Attention Negativity (ADAN)

Elicited during a cue-target interval, the anterior directing attention negativity (ADAN) is the second in order, but perhaps the most intriguing lateralized component. It is maximum over frontal electrodes and it reflects the enhanced negativity, which is observed between 300 to 500 ms after the informative cue, contralaterally to the attentional shift induced by the cue (Mangun, 1994 in Hopf and Magnun, 2000). The dorsal premotor cortex (PMd) is the most likely generator of the ADAN (Praamstra et al., 2005; Mathews et al., 2006), although contributions of the frontal eye fields (FEF) should also been taken into account (Van der Lubbe et al., 2006).

The ADAN was originally considered to result solely from covert shifts of visuospatial attention evoked by the informative cue (e.g. Hopf and Mangun, 2000; Nobre et al., 2000). However, later studies (Eimer and van Velzen, 2002; Eimer et al., 2002, 2003b) demonstrated that the ADAN can be elicited when auditory cues direct attention towards relevant auditory or tactile stimuli, even when the allocation of spatial attention is performed in darkness (Eimer et al., 2003b). These results suggest that the ADAN reflects supramodal mechanisms of spatial attention orienting. It should be noted

that (Green et al., 2005) and (Green and McDonald, 2006) challenged this view, since no ADAN was observed in the interval between auditory cue and auditory or visual target stimuli. However, in a recent study, Seiss et al. (2007) employed a paradigm analogous to Green et al. (2005) and clearly demonstrated that ADAN can be elicited in unimodal auditory task. The authors attributed the discrepant results of Green et al. (2005) to inadequate selection of electrode pairs for the quantification of the ADAN.

The ADAN is also elicited during preparation of saccade movements (Wauschkuhn et al., 1997; Van der Lubbe et al., 2000; Eimer et al., 2006). Van der Lubbe et al. (2006) argued that the allocation of spatial attention can be interpreted as tendency to perform or inhibit a saccade movement. Although this view seems plausible, it cannot sufficiently explain the presence of the ADAN when a task is executed in darkness (Eimer et al., 2003b). Importantly, Van Velzen et al. (2006) reported the occurrence of the ADAN in a tactile attention task for congenitally and early blind participants. This suggests that the ADAN is generated by attentional mechanisms operating within a somatotopically defined spatial frame of reference. In an earlier study, Eimer et al. (2003a) employed a paradigm where the participants had to detect tactile stimuli having their hands either crossed or uncrossed, therefore inducing a discrepancy between the visually and somatotopically mediated spatial frames of reference. Interestingly, the polarity of the ADAN was reversed with crossed hands, indicating that the ADAN, in agreement to Van Velzen et al., (2006) view, primarily reflects somatotopically based attentional mechanisms.

The ADAN, apart from orienting attention in space, is also elicited by the selection of the responding hand (Verleger et al., 2000a; Eimer et al., 2005; Mathews et al., 2006; Eimer and van Velzen, 2006). Praamstra et al. (2005) showed that response preparation and spatial attention orienting originate from common mechanisms within the fronto-parietal attention network. In this study, the ADAN was essentially the same in morphology and topography when the participants were instructed either to direct spatial attention towards to a left or to a right target location with or without preparing a response or to prepare a response without directing spatial attention. In addition, the authors, by elucidating the similarity in latency and amplitude of the ADAN with the P300 component, suggested that the ADAN may represent the focal lateralization of the P300. The P300 is considered to be an inhibitory potential, related to stimulus evaluation and context updating. The authors proposed that cue-induced orienting of attention and response selection may involve the "inhibition of the rejected behavioural options".

The participants in all the above mentioned studies were required to respond by performing simple movements, such as pressing a button. Berndt et al. (2002) reported premotor lateralized activity (equivalent to the ADAN) in a study where participants had to prepare pointing movements towards random or sequential, peripherally or centrally presented visual targets. Movement direction affected the latency of this component, while its amplitude was smaller when the direction of the cue was predictable. A drawback of this study was that only one hand was used within a block, so it was not possible to attribute these effects to effector selection or movement direction selection. Gherri et al. (2007) addressed this issue by instructing the participants to produce leftward or rightward reaching movements towards targets located to the left or to the

right hemispace (both hands were used within a block). An interesting finding was that an ADAN was elicited even from cues, which conveyed only partial information for the expected movement (i.e. specification of either movement direction or responding hand). In addition, the ADAN was not present in the case of inwards movements (e.g. right hand going towards the left hemispace), which presumably reflected the fact that the spatially incongruent selection of movement direction and responding hand resulted in lateralized activities of opposite polarity, which effectively cancelled each other. The authors argued that their findings indicate that the ADAN reflects lateralized activities, probably within the PMd, which independently specify spatial parameters of an externally cued reaching movement.

1.8.4.3. Late Directing Attention Positivity (LDAP)

The late directing attention positivity (LDAP) is a lateralized component which develops over posterior sites around 500-600 ms after the precue stimulus (Harter et al., 1989) as a result of an increased posterior positivity, contralateral to the side of the attended stimulus.

The LDAP is most likely generated in the occipitotemporal cortex (Praamstra et al., 2005; Mathews et al., 2006). Van der Lubbe et al. (2006) suggested that the LDAP might originate from the ventral intraparietal sulcus, however the discrepant results between two source analyses performed in that study, one with fixed and another one with free dipole locations, challenge the validity of their assumption. Nevertheless, an

early small contribution of the parietal cortex to the LDAP, preceding the occipitotemporal activation, cannot be entirely ruled out (Praamstra et al., 2005).

The LDAP was originally considered to be elicited only by shifts of visuospatial attention (e.g. Harter et al., 1989; Yamaguchi et al., 1994; Hopf and Mangun, 2000). Later studies showed that this component is also elicited by tactile and auditory stimuli, suggesting that the LDAP may reflect supramodal attentional processes (Eimer and van Velzen, 2002; Eimer et al., 2003b; Green et al., 2005; Green and McDonald, 2006; Seiss et al., 2007). In addition, the LDAP has been observed during manual response preparation (e.g. Eimer et al., 2005; Praamstra et al., 2005) and covert saccade preparation (e.g. Wauschkuhn et al., 1997; Eimer et al., 2006), indicating a link between these processes and attentional shifts (Rizzolatti et al., 1994). It is also present during preparation of reaching movement, showing a stronger dependency on effector rather than direction selection (Gherri et al., 2007).

Praamstra et al. (2005), based on the localization of the LDAP sources within the occipitotemporal cortex, postulated that the LDAP may reflect an integrating mechanism of visual, spatial attention and motor signals, which is related to the updating of the actor's body representation. It should be noted though, that the LDAP was attenuated (Eimer et al., 2003b) or even absent (van Velzen et al., 2006) in tasks where tactile attention was allocated in darkness. Futhermore, the LDAP was absent in early and congenitally blind participants (van Velzen et al., 2006). These findings suggest that the LDAP, even if non-visual stimuli are task-relevant, depends mostly on visually defined spatial encoding.

1.9. Movement-related changes in the alpha and beta frequency bands

Preparation for action induces changes in the amplitude of brain oscillations, which have distinct functional roles depending on the frequency band in which they occur. The most commonly studied brain rhythms in motor control lie in the alpha and the beta frequency range.

1.9.1. Alpha Event Related Desynchronization/Synchronization (ERD/ERS)

Task-induced frequency specific changes (ERD/ERS, see Section 1.3.2.) in the alpha band (7-13 Hz) are recorded in a variety of motor and cognitive tasks and are typically observed over frontal, parietal and motor areas. Alpha oscillations are controlled by a thalamo-cortical network (Pfurtscheller, 2006), although task-related modulation in the alpha band has been also found in subcortical structures such as the reticular formation and the hippocampus (Klimesch et al., 2007). Alpha ERD is not a unitary phenomenon (Pfurtscheller and Lopes da Silva, 1999; Klimesch et al., 2007). ERD in the lower alpha band (7-10 Hz) is topographically widespread and is associated with almost all types of task, most likely reflecting general unspecific attentional demands (Klimesch et al., 1997; Pfurtscheller, 2003). On the other hand, upper alpha ERD (10-13 Hz) is topographically more focused and is related to semantic processing (Pfurtscheller, 2003; Klimesch et al., 2007).

The traditional view is that the alpha rhythm is associated with cortical "idling" and its decrease in amplitude indicates cortical activation (for a review, Pfurtscheller and

Lopes da Silva, 1999). However, recent studies have shown that alpha ERD/ERS also depends on the level of consciousness (Pfurtscheller, 2006), task performance (Vogt et al., 1998; Klimesch et al., 1999; Hanslmayr et al., 2005) and intelligence/IQ score (Neubauer et al., 1995; Doppelmayr et al., 2005). In motor tasks, alpha ERD is recorded over sensorimotor areas before and during self-paced or externally triggered movements (Pfurtscheller and Berghold, 1989; Filipovic et al., 2001; Alegre et al., 2003a), motor observation (Babiloni et al., 2002) or motor imagery (Neuper and Pfurtscheller, 2001a; Kilner et al., 2006). It starts around 2 seconds prior to movement onset, being initially stronger over contralateral rolandic areas and it gradually becomes symmetric just before movement execution (Pfurtscheller and Lopes da Silva, 1999). Interestingly, the time course and the topography of alpha ERD does not depend on the duration (Stancák, Jr. and Pfurtscheller, 1996) or the type of movement (Pfurtscheller et al., 1998), a property which indicates a rather unspecific preparatory state of sensorimotor areas.

In motor tasks, the amplitude decrease of alpha oscillations is often followed by a short lasting increase, which according to the traditional view of "cortical idling", denotes a deactivated cortical network (Pfurtscheller and Lopes da Silva, 1999). Contrary to this view, recent studies have provided strong evidence that the enhancement of alpha oscillation results from a top-down mechanism, which is related to active inhibition and timing of cortical processing (for a review, Klimesch et al., 2007). The presumed inhibitory role of alpha ERS was supported by findings in various cognitive and motor tasks, where alpha ERS was recorded over task-irrelevant brain areas or when a response had to be withheld (Pfurtscheller and Neuper, 1994; Gerloff et al., 1998; Worden et al., 2000; Hummel et al., 2002). In this line of argument, the gradual build-up of alpha ERD

reflects the cessation of inhibition in certain task-relevant cortical areas in order for active information processing to take place.

1.9.2. Beta Event Related Desynchronization/Synchronization (ERD/ERS)

Similarly to the alpha rhythm, the amplitude of beta-band (13-30) Hz is modulated during motor tasks. A decrease in amplitude (i.e. ERD) is normally observed during self-generated (Chatrian et al., 1959; Stancák, Jr. and Pfurtscheller, 1996; Cassim et al., 2000) or externally paced (Leocani et al., 2001; Alegre et al., 2003a; Gómez et al., 2004b) movements, movement observation (Babiloni et al., 2002; Muthukumaraswamy et al., 2004) and movement imagery (Pfurtscheller and Neuper, 1997; McFarland et al., 2000). In the case of movements with predictable time onsets, ERD starts around 1.5 s prior to the movement in motor areas contralaterally to the responding hand and it gradually becomes bilateral during movement execution (Alegre et al., 2003a; Calmels et al., 2006; Wheaton et al., 2008).

Beta ERD is typically followed by a rather controversial increase (synchronization), often termed post-movement beta ERS (Pfurtscheller et al., 1996) or beta rebound (Salmelin and Hari, 1994a). It usually peaks around 1s after movement onset and, unlike beta ERD, it depends on movement parameters (Stancák Jr. and Pfurtscheller, 1996) and the type of the effector (Pfurtscheller et al., 1999b). Several EEG and MEG studies have consistently demonstrated that, at the cortical level, beta ERS has a somatotopical distribution and it originates precentrally, mainly from the primary motor

cortex with possible small contributions from supplementary and lateral premotor areas (Salmelin et al., 1995; Pfurtscheller et al., 1996; Ohara et al., 2001; Sochůrková et al., 2006; Jurkiewicz et al., 2006). Parkes et al. (2006) on the other hand, in a combined EEG-fMRI study argued that the generators of beta ERS are located near the postcentral sulcus. However, several methodological issues of that study question the validity of these findings (see also, Jurkiewicz et al., 2006). First, due to high levels of noise, the authors were able to identify beta ERS in the on-line EEG-fMRI recordings only in two subjects; for this reason they used EEG data recorded outside the scanner. Also, correlations between the beta ERS and the blood oxygenation level dependent (BOLD) response were calculated based on EEG data acquired only from the electrode C3. Furthermore, when looking at normalized data, beta ERS correlated strongly with BOLD activity in the motor cortex rather than BOLD activity in post-central regions. Finally, it is likely that, in general, the BOLD response can also be correlated to other EEG components, for example to alpha oscillations, the (quite often stronger) modulation of which follows a similar time course to beta oscillations.

Regarding the functional significance of beta oscillations, it has been proposed that they play an antikinetic role (Kühn et al., 2004; Brown and Williams, 2005) and that they reflect the preservation of the current motor state (Gilbertson et al., 2005). Consequently, the amplitude decrease of beta oscillations (i.e. ERD) signifies activation (either facilitation or inhibition, see Leocani et al., 2001) of brain areas, which facilitate the transition to a new motor state. The interpretation of beta ERS, however, is still debated. Initially, it was believed that it simply reflects a deactivated motor network (cortical "idling", see Pfurtscheller et al., 1996; Chen et al., 1998), independently of

sensory feedback (Leocani et al., 2001). In contrast, other studies suggest that beta ERS is an active inhibitory process which requires sensory feedback (Cassim et al., 2001; Kühn et al., 2006) and signifies the re-establishment of the previous postural state (Brown and Williams, 2005). It is possible though that these views are complementary rather than contradictory; it has been proposed that multiple beta rhythms may exist pre- and possibly post-centrally, each with a different functional significance (Feige et al., 1996; Cassim et al., 2000; Jurkiewicz et al., 2006).

1.10. Overview of experiments

The objective of our experiments was to study the neural mechanisms of action preparation by utilising the advantages offered by electroencephalography. For this purpose, we employed "traditional" ERP analyses, as well as analyses of oscillatory phenomena (ERD/ERS and steady-state ERPs) and source localization techniques (minimum norm approach, dipole source analysis and beamformer imaging).

1.10.1. Temporal Preparation

The purpose of temporal preparation (see Section 1.4.2) is the estimation of the occurrence in time of an anticipated external event and/or the timing of the execution of a prepared action. In the case of stimulus-driven responses, the optimal strategy for a person would be to reach a state of maximum preparation exactly at the time of the

presentation of the corresponding stimulus. Usually, the control and production of a timed response is guided by explicit experimental manipulations of time. However, timing can also occur in an implicit manner, being an emergent property of motor performance, in other words a product of behaviour while the motor system controls certain kinetic or kinematic parameter(s) of the response. Zelaznik and colleagues (Zelaznik et al., 2000, 2002, 2005) argued that the performance of periodic discrete movements (e.g. tapping) requires an explicit representation of time (also termed "event timing") whereas continuous movements (e.g. circle drawing) rely on implicit timing (also termed "emergent timing") processes. The authors conclude that the timing of the duration of a movement is an implicit process, whereas the initiation of a movement an explicit one.

It is clear, however, that there are alternative ways of dissociating explicit and implicit timing processes. In the first experiment (Chapter 2) of the present thesis we examined the temporal preparatory processes related to the performance of discrete responses in a choice-reaction task (i.e.. button pressing with either the index or the middle finger) instructed by periodically presented visual stimuli. The stimuli were presented in two different, temporally regular patterns with the occasional addition of deviant (shorter or longer) time intervals. The participants were instructed to respond swiftly after the presentation of a visual stimulus which also designated the responding finger. Hence, the encoding of the duration of the interstimulus interval was not necessary for the correct performance of the task; instead it was expected to occur in an implicit manner.

Our aim was to study the associated neural processes of implicit timing and compare them to the ones utilized in explicit timing tasks. Previous EEG studies have associated features (i.e. slope, peak time) of the Contingent Negative Variation (CNV, see Section 1.8.2) with the estimation of the duration of a time interval (cf. Pfeuty et al., 2005). The adjustment of the CNV to the temporal requirements of a task is similar to the behaviour of the "climbing neuronal activity" which is considered a neural correlate of encoding of time intervals (Durstewitz, 2004). Similarly in our experiment, the slope of the CNV varied with the length of the interstimulus interval. Importantly, the CNV peaked at the time of an expected stimulus even when the stimulus was delayed, suggesting that the CNV reflects the duration of a stored time interval. Furthermore, the modulation of the preparatory alpha and beta activity demonstrated the influence of implicit timing in perceptual processing and motor preparation. In addition, source analyses suggested premotoric origins for both the late CNV and the beta ERS components, which in the case of the CNV were different than the ones reported in explicit timing tasks.

Temporal preparation was also the theme of the second experiment (Chapter 3) of the present thesis; however, contrary to Chapter 2, the temporal estimation regarding the occurrence of an external event was crucial for the correct performance of the task. In this experiment, participants were required to hold in precision grip (i.e. index finger opposed to thumb) a manipulandum and to resist to vertically directed loads presented either in regular (periodical) or random time intervals, by a robotic arm connected to the manipulandum. Our objective was to compare the preparatory processes that take place when a person can adequately estimate the time of an expected event (i.e. equally spaced

time-intervals) against a condition where a person is in a state of temporal uncertainty regarding the time of the presentation of the same event (i.e. randomly spaced time-intervals). In the former case, the participant could form a time-specific motor plan, whereas in the later case he/she was in a state of rather diffuse motor preparation, which led to a largely reflexive response.

These processes were studied by means of EEG recordings, grip and load forces, as well as EMG signals recorded from relevant muscles. At the peripheral level, slowly rising grip force and EMG activity developed prior to load onset, solely in the regular condition, accompanied by a corresponding amplitude modulation of slow brain preparatory activity. In addition, an important finding of this study was that the amplitude modulation of the long latency reflex (LLR) was preceded by a comparable modulation of primary motor cortex activation, providing evidence for the existence of a transcortical loop, which contributes at least partially to the LLR generation.

1.10.2. Event Preparation

Preparing to act at a specific point in time constitutes one part of preparation for action; the other part being the selection of the appropriate features, which will form the required response. The latter type of preparation is called "event preparation" (see also Section 1.4.2) and is usually studied by means of the movement precuing paradigm (Goodman and Kelso, 1980; Rosenbaum, 1980), in which response selection depends upon the information provided by the precue stimulus. This paradigm was employed in our third

experiment (Chapter 4) where participants had to prepare a left or right hand response (i.e. button press) as indicated by preceding directional arrows and to perform it when an informative stimulus instructed them to do so. The foreperiod interval was kept constant, therefore, as demonstrated in Chapter 2, implicit temporal preparation processes presumably took place, peaking around the time of the imperative stimulus.

However, in this experiment, we were specifically interested to study the mechanisms of event preparation, as reflected in movement-related lateralized potentials (i.e. ADAN and LRP), developing during the preparatory period of a choice-reaction task. For this purpose we used continuous electrical stimulation, applied bilaterally on the median nerve of the wrists, which resulted in steady-state somatosensory evoked potentials (ssSEPs) oscillating at the frequency of the driving stimuli. The methodological novelty of this study was that all the analyses were performed at the source level. The amplitudes of the dipole sources generating the ssSEPs were modulated before and during response execution due to premotor and primary cortex activation (see "sensorimotor gating", Section 1.3.1). In particular, ssSEPs amplitude displayed an asymmetrical decrease during the occurrence of the ADAN, suggesting that this component is probably generated due to higher activation of the hemisphere contralateral to the response.

Finally, in Chapter 5, we examined the preparatory processes that take place when a person faces multiple response options. Here, the precue stimulus provided graded information about the direction of the required reaching movement, thus varying the degrees of (un)certainty regarding the preparation of the appropriate response. Recent

research in primates (Bastian et al., 2003; Cisek and Kalaska, 2005) demonstrated that when primates face multiple movement options, they prepare simultaneously for all possible outcomes. Such results suggest that specification of movement parameters and response selection occur in a parallel manner within the same neural substrates, primarily the PMd, PPC and in a lesser degree M1 (Cisek, 2006, 2007)

Our study consisted of a bimanual choice-reaction task, in which a precue stimulus pointed towards one, two or three potential adjacent targets, followed by an imperative stimulus which fully specified the direction of the movement. Reaction times as well the amplitudes of (pre)motoric EEG components (ADAN, LRP and CNV) were modulated with the respect to the level of event uncertainty (i.e. movement direction). Our results support the notion that competing representations of multiple response options exist simultaneously in the PMd as well as in the MI. Moreover, we recorded partially lateralized parietal activity preceding premotor activation (i.e. the ADAN); an intriguing finding, which adds to the debate regarding the temporal order in which frontal and parietal areas form networks related to attention and response preparation.

Chapter 2

Neurophysiology of implicit timing in serial choice- reaction time performance

* A modified version of this chapter has been published as:

Praamstra P, Kourtis D, Kwok HF, Oostenveld R (2006) Neurophysiology of implicit timing in serial choice-reaction time performance. J Neurosci 26:5448-5455.

Abstract

Neural representations of time for the judgment of temporal durations are reflected in electroencephalographic (EEG) slow brain potentials, as established in time production and perception tasks. Here, we investigated whether anticipatory processes in reaction-time procedures are governed by similar mechanisms of interval timing. We used a choice reaction task with two different, temporally regular stimulus presentation regimes, both with occasional deviant interstimulus intervals. Temporal preparation was shown in the form of adjustments in time course of slow brain potentials, such that they reached their maximum amplitude just before a new trial, independent of the duration of the interstimulus interval. Preparation was focused on a brief time window, demonstrated by a drop in amplitude of slow potentials as the standard interval had elapsed in deviant interstimulus intervals. Implicit timing influencing perceptual processing was shown in reduced visual-evoked responses to delayed stimuli after a deviant interstimulus interval and in a reduction of EEG power over the visual cortex at the time when the standard interval had elapsed. In contrast to explicit timing tasks, the slow brain potential manifestations of implicit timing originated in the lateral instead of the medial premotor cortex. Together, the results show that temporal regularities set up a narrow time window of motor and sensory attention, demonstrating the operation of interval timing in reaction time performance. The divergence in slow brain potential distribution between implicit and explicit timing tasks suggests that interval timing for different behaviours relies on qualitatively similar mechanisms implemented in distinct cortical substrates.

2.1. Introduction

The objective of temporal preparation is the enhancement in behaviour when the timing of the planned action is uncertain (Leuthold et al., 2004). Correct timing is crucial, since preparation for a response can be sustained at an optimal level only for a few hundred milliseconds (Alegria, 1974). A common notion is that the locus of temporal preparation lies within the motor system (for a review see, Müller-Gethmann et al., 2003). This association comes into agreement with the natural propensity for rhythmicity in the motor system (Grosjean et al., 2001); however temporal preparation is also likely to be mediated by sensorimotor integration (Janssen and Shadlen, 2005) or even sensory processes (Ghose and Maunsell, 2002).

The majority of experimenters so far have studied the neural basis of temporal preparation using paradigms where timing directly guided task performance (i.e. explicit timing tasks). Several EEG studies have extensively examined the Contingent Negative Variation (CNV), a cortical electrophysiological signal which develops progressively during the time period between a warning stimulus and a subsequent imperative stimulus (Walter et al., 1964). The CNV is as long-latency, slow wave of negative polarity, which has an early component, recorded over frontocentral areas and a later one maximal over centroparietal areas (Rohrbaugh et al., 1976), which overlap in short (< 3-4 sec) interstimulus intervals (Rosahl and Knight, 1995). Imaging as well as animal studies suggest that CNV results from activity generated within a thalamo-cortical-striatal network (Komura et al., 2001; Macar and Vidal, 2003; Nagai et al., 2004).

A CNV is typically recorded in tasks when subjects are required to reproduce an interval or to judge the duration of a given interval relative to a memorized one (Ruchkin et al., 1977; Macar et al., 1999; Pouthas et al., 2000; Pfeuty et al., 2003). The peak and the latency of CNV termination correlate with the reproduced duration (Ruchkin et al., 1977) and in discrimination paradigms, with the perceived duration of a target interval (Macar et al., 1999). The notion that the CNV reflects temporal encoding is supported by the finding that the CNV develops and peaks at the end of a memorized standard and afterwards starts to decline while the current stimulus continues (Macar and Vidal, 2003; Pfeuty et al., 2003). Contrary to CNV peak latency, the CNV peak amplitude does not depend on the duration of the memorized interval; due to CNV slope adjustments, it remains the same for short and long intervals (Pfeuty et al., 2005).

Encoding of time intervals may be represented at a neuronal level in the form of "climbing neuronal activity" (Durstewitz, 2003, 2004; Reutimann et al., 2004), whose slope is inversely proportional to interval length and its peak time coincides with the occurence of an upcoming anticipated event. The similarity between the properties of the "climbing neuronal activity" and the CNV indicates a link between the two processes, which are compatible with the existence of an internal pacemaker/accumulator (Pfeuty et al., 2005). The medial frontal cortex, in particular the supplementary motor area, has been proposed as the neural substrate of timing functions reflected in the CNV (Macar et al., 1999; Pfeuty et al., 2005).

A different approach for investigating motor preparation is the analysis of EEG signals in the frequency domain, more specifically, the study of task-dependent

modulations of the ongoing EEG activity within certain frequency bands. The decrease of the EEG power/activity in a given frequency band is called Event-Related Desynchronization (ERD), whilst the power/activity increase is called Event-Related Synchronization (ERS) (Pfurtscheller and Lopes da Silva, 1999). ERD in the alpha (8-12 Hz) and the beta (12-30 Hz) bands has been typically recorded over sensory and motor cortical areas before self-paced movements and before the occurrence of an expected stimulus. Beta ERD is always followed by a beta ERS component, occurring after movement onset and it is usually observed over primary motor and premotor areas (Cassim et al., 2000; Filipovic et al., 2001; Alegre et al., 2003a; Gómez et al., 2004b; Alegre et al., 2006). The functional meaning of this component (often termed beta rebound) is still debatable. It is believed that beta ERS reflects a state of "motor cortex idling" (Pfurtscheller et al., 1996), which results from the removal of corticospinal activation and inhibition (Leocani et al., 2001); however, it is possible that it also depends on sensory afferent inputs (Cassim et al., 2001). Alternatively, beta ERS may reflect the "resetting" of the underlying cortical networks (Pfurtscheller et al., 2005).

The present study investigated whether the implicit timing that is manifested in the automatic adjustment of subjects to the temporal structure of a task is supported by interval timing mechanisms similar to those identified in explicit timing tasks. The questions addressed were, first, whether the timing features reflected in slow brain potentials are preserved under implicit timing conditions, and second, whether their distribution supports the same neural substrate as for explicit timing functions. Implicit timing processes were investigated by means of a comparison between two different

stimulus presentation regimes and by perturbing a standard interstimulus interval by a deviant interval.

2.2. Methods

2.2.1. Participants

Ten participants (7 men; age 34 ± 9 yr), all of whom were right-handed according to self-report, took part in the experiment. All had normal or corrected-to-normal vision. Informed consent was obtained and the investigation was approved by the department's ethical review board.

2.2.2. Procedures and stimuli

The experiment consisted of a choice reaction task where participants responsed to arrow stimuli presented on a computer screen. Participants had to indicate the direction of left or right pointing arrows by pressing one of two buttons. The experiment was divided in 8 blocks of ~6 minutes each. Within each block, individual trials were presented in series of 11, 13, 15, 17, 19, or 21 trials. In each series the stimulus-onset-asynchrony (SOA) between successive reaction stimuli was either 1.5 s or 2.0 s, except for the last SOA which was always 1.75 s, that is 250 ms shorter (short deviant) or longer (long deviant) than the preceding SOAs (Figure 2.1). Trial sequences with long and short SOAs followed each other randomly with pauses of 8 seconds between them to give participants

time to blink. The total number of sequences presented was 96, equally divided in short and long SOA series. Responses were made with the index or middle finger depending on the direction of the arrow, which pointed to the left or right with equal probability. Participants started the experiment with the left or right hand and switched response hand every two blocks. Half of the participants started with the left, the other half with the right hand. The experiment was preceded by a short practice block that contained sequences with long and short SOAs. Participants were not made aware of the deviant final SOA. They were debriefed after the experiment and asked whether they had been aware of any temporal irregularity other than the different SOAs between series. Subsequently, they were told about the deviant SOAs and asked again whether they had noticed this feature.

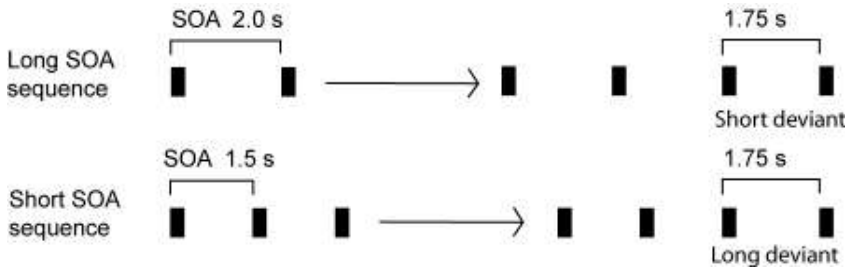

Figure 2.6: Schematic of the long and short SOA trial sequences. Stimuli were presented in short series of 11, 13, 15, 17, 19, or 21 trials. Each series of stimuli had SOAs of either 1.5s or 2.0s, except for the last SOA which was always 1.75s.

The experiment was run in a normally illuminated room. Stimuli were presented on a 17 inch monitor at a resolution of 800 x 600. Participants were seated comfortably in an armchair with their eyes 100 cm from the monitor. Response keys were attached to the armrests of the chair and subjects rested their index and middle fingers on the keys. The stimuli were presented in white on a grey background for a duration of 200 ms. A fixation area was indicated by permanently displayed brackets surrounding the central screen area where the arrow stimuli were presented. The brackets enclosed a square of 1° x 1° of visual angle; the arrows measured 0.75° x 0.75° of visual angle.

2.2.3. EEG recording, data processing and analysis

EEG was recorded continuously with Ag/AgCl electrodes from 128 scalp electrodes relative to an (off-line) averaged left and right mastoid reference. The electrodes were placed according to the 10-5 electrode system (American Electroencephalographic Society, 1994; Oostenveld and Praamstra, 2001) using a nylon electrode cap. Eye movements were monitored by bipolar horizontal and vertical EOG derivations. EEG and EOG signals were amplified with a band pass of 0-128 Hz by BioSemi Active-Two amplifiers and sampled at 512 Hz. The continuous EEG recordings were off-line segmented in 3000 ms epochs starting 500 ms before stimulus onset and spanning one intertrial interval. Subsequently, separate averages were constructed for short and long SOA conditions performed with the left and with the right hand. To capture the preparatory activity at a time when participants were adjusted to the series' fixed SOA, these averages only included the last 8 SOAs (before the final deviant SOA) of each

series. Averages of the final deviant SOAs were constructed separately for short deviant and long deviant SOAs, but collapsed across response hands given the small number of deviant trials (48 short and 48 long deviants, each divided in 24 trials per hand). For all averages, the prestimulus baseline was aligned to zero, by subtracting the mean signal amplitude in the interval from -500 to 0 ms. For the analysis of event-related potentials, individual trials containing eye movement artefacts or blinks were rejected. For analyses of event-related changes in spectral power in Brain Electrical Source Analysis (BESA; MEGIS; Gräfelfing; Germany) (see below), eye movement and blink artifact were corrected using a multiple source analysis approach (Berg and Scherg, 1994).

Event-related potential amplitudes were analyzed by pooling the values of neighbouring electrodes within regions of interest, identified on the basis of the scalp topography. Thus, the amplitude and slope of the CNV were analyzed in ROIs overlying the left and right premotor region (C3/4, FC3/4, FCC3/4h and FCC5/6h). The slope of the CNV was derived from the mean amplitudes measured between 600-700 ms and 1400-1500 ms (short SOA condition), and from the mean amplitudes measured between 600-700 ms and 1900-2000 ms (long SOA condition). Analyses on the slope of the CNV in deviant trials included additional ROIs overlying the centroparietal region (Pz, POz, PPO1h and PPO2h), and left and right occipitotemporal region (PO7/8, P7/8, POO9/10h and PPO9/10h). Here, slopes were quantified by fitting a linear regression line to data points between 1600 and 1800 ms.

For analysis of event-related changes in spectral power, epochs were further processed to obtain temporal-spectral-evolution (TSE) waveforms (Salmelin and Hari,

1994b). To generate TSE waveforms, the individual epochs were first band-pass filtered for frequency bands of interest, using Butterworth zero phase-shift filters (24 dB/octave). The filtered epochs were then rectified before averaging to prevent phase cancellation. The resulting average waveforms represent the time-varying magnitude of activity in the selected frequency band. This report will refer only to findings in the alpha band TSE waveforms (8-12 Hz) that discriminated between the processing of short and long deviant SOAs.

In addition to the TSE analysis, a more comprehensive analysis of event-related spectral perturbations was performed using BESA (Brain Electrical Source Analysis). After segmentation and artifact correction, each single trial was transformed in the time-frequency domain using complex demodulation set to a frequency resolution of 1 Hz and temporal resolution of 50 ms in the frequency range 2-50 Hz. Time-frequency representations per channel and participant were created by averaging spectral density amplitude over trials. Individual participant and grand average representations for short and long SOA conditions revealed a pronounced modulation of beta activity in the intertrial interval. The beta activity modulation was first analyzed at the sensor level by pooling the activities recorded from five adjacent electrodes sites overlying the left and right premotor region (C1/2, C3/4, FCC3h/4h, FC1/2 and FC3/4).

Beta activity modulation was localized using a beamformer analysis. The BESA beamformer is a modified version of the linearly constrained minimum variance vector beamformer in the time-frequency domain as described in Gross et al. (2001). The beamformer operator is computed using the cross spectral density matrix (the time-

frequency equivalent of the data covariance matrix) computed from the single-trial data. This allows to image evoked as well as induced oscillatory activity in a user-defined time-frequency range, where time is taken relative to a triggered event. In beamforming analyses, the whole brain is scanned voxel per voxel. The activity at each voxel is computed by applying a spatial filter to the data. The time course of beta modulation was analyzed using an ROI analysis and compared in time windows 850-1150 ms and 1150-1450 ms post-stimulus against a 300 ms pre-stimulus baseline. Two ROIs were defined in left and right motor cortex, each including the voxels within a 10 mm radius of the grand average activation maxima in the contralateral and ipsilateral motor cortex. The averaging of time-frequency as well as beamformer data was conducted using FieldTrip, a MATLAB toolbox for EEG/MEG analysis, developed by F.C. Donders Centre (FCDC) in Nijmegen, Netherlands.

The cortical sources of slow brain potentials were estimated with a distributed multiple source modeling technique (minimum norm approach), implemented in BESA. The approach involves the computation of the source activities of a large number of regional sources evenly distributed over 1420 standard locations of the smoothed surface of a standard brain. A unique current distribution over this predetermined layer of regional sources, explaining the surface measurements, is obtained by applying the minimum norm constraint which selects the solution with minimum overall intensity (Hämäläinen and Ilmoniemi, 1994). The obtained solutions were robust under different weighting options.

Reaction time analyses were performed on the responses to trials following a deviant SOA, as well as on the eight trials preceding the deviant. The responses to these eight trials were averaged to obtain a mean value for short standards and long standards, respectively. EEG and reaction time data were analyzed using ANOVA in SigmaScan Pro software (SPSS, Chicago, IL).

2.3. Results

2.3.1. Response times

The participants were debriefed after the experiment to evaluate whether they had been aware of the deviant final SOAs. Although none of the participants had noticed the timing perturbations, evidence of breaches of temporal expectation was reflected in slower reaction times, i.e. 377 ± 25 ms vs. 365 ± 25 ms ($F(1,9)=7.01$, $p<0.05$) for the 'long deviants' relative to their 1.5s standards, and 373 ± 30 ms vs. 365 ± 25 ms ($F(1,9)=14.90$, $p<0.01$) for the 'short deviants' relative to their 2.0s standards. Error rates were between 2.7 and 5.2 % for responses after standard and deviant SOAs, with no significant difference between conditions.

2.3.2. Neurophysiology

2.3.2.1. Effects of SOA on slow preparatory brain potentials

If CNV-like slow preparatory brain potentials that develop between successive trials are influenced by an implicit timing mechanism similar to what has been described in explicit timing tasks, then their time course should be different for short and long SOA conditions, such that the amplitude reached before the next trial is the same in short and long SOA conditions. In contrast, if they are not under the control of such a timing mechanism, the peak amplitude should be higher for long SOAs than for short SOAs, because the CNV will continue to rise. To evaluate these contrasting hypotheses, the CNV topography was determined in the last 100 ms preceding the next trial (i.e. in windows from 1400-1500 ms and 1900-2000 ms for the short and long SOA conditions, respectively). The CNV amplitude was subsequently quantified in two groups of four electrodes over left and right premotor region, where the CNV reached its maximal amplitude.

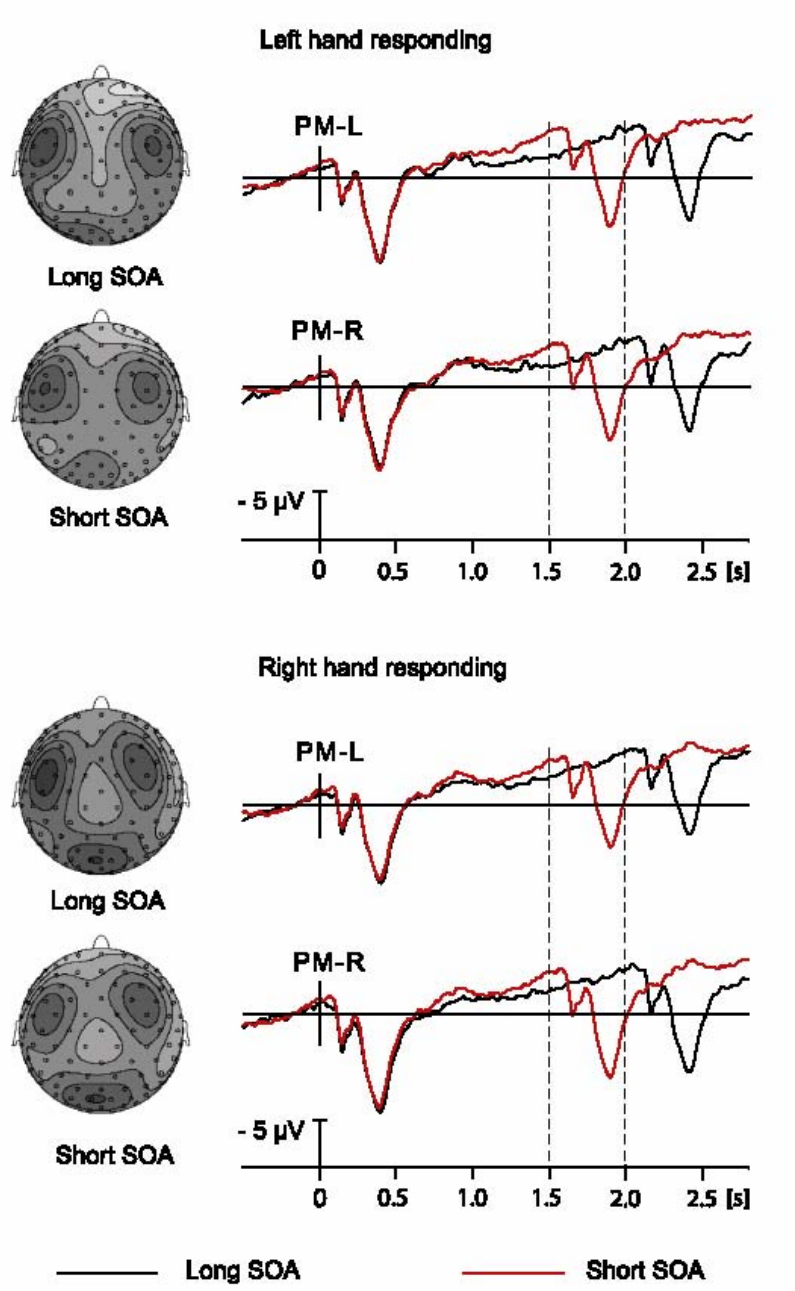

Figure 2.7: Scalp topography and CNV waveforms in short and long SOA conditions separately for left (top) and right (bottom) hand response blocks. Waveforms represent average activity of four electrodes overlying the left (PM-L) and right (PM-R) premotor region activation maxima. Line spacing in the scalp maps is 0.5 µV. The dashed lines indicate the 1500 ms and 2000 ms SOA durations.

The CNV slope is adjusted to the duration of the SOA, and the CNV reaches the same amplitude before the next trial regardless of the SOA (Figure 2.2). This was expressed in an absence of an effect of SOA ($F(1,9)=1.23$, $p=0.30$). Comparing the short and long SOA conditions, the CNV rose steeper for the short than for the long SOA condition ($F(1,9)=7.70$, $p=0.022$). In neither of the analyses did the CNV differ between hemispheres, nor was it modulated by the side of the response ($Fs \leq 1$). The latter finding indicates that the timing reflected in the CNV is not simply preparation of the response hand.

These results show that the CNV developing between successive reaction stimuli reaches a fixed amplitude just before the anticipated termination of the entrained interval. This amplitude is independent of the duration of the interval, because the CNV adjusts its slope to the duration of the interval after repeated exposure.

2.3.2.2. Effects of timing perturbations on slow preparatory brain potentials

Passive entrainment with a regular interstimulus interval produced a similar modulation of the CNV in the deviant final interstimulus interval when the deviance consisted of a lengthening of the regular SOA (Figure 2.3).

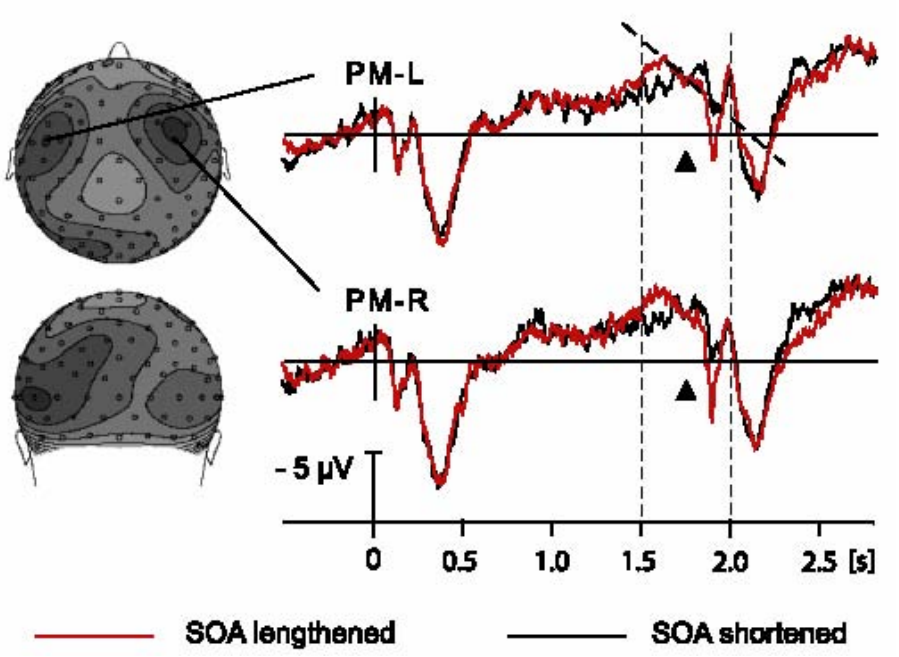

Figure 2.8: Effect of timing perturbation on slow brain potentials. The topography of the CNV in the long deviant condition (1400-1500 ms) is similar to the topography seen with regular SOA. The CNV over left and right premotor areas peaks around 1600 ms, i.e. shortly after the expected time of stimulus arrival, and drops in amplitude before stimulus presentation at 1750 ms. The dashed lines indicate the expected 1500 ms and 2000 ms SOA durations. In the top traces, a regression line is fitted to the downgoing slope of the CNV in the long deviant condition. Line spacing in the scalp maps is 0.5 µV.

The CNVs of long and short deviant SOAs show a different rise time because of the preceding entrainment with short and long standard SOAs, respectively. The CNV of the short deviant SOA shows a steady rise until the presentation of the reaction stimulus at 1750 ms. Crucially, the CNV of the long deviant SOA reached maximum amplitude

around 1600 ms (i.e. 100 ms later than the expected arrival of the stimulus, but still 150 ms before the actual stimulus). To quantify the difference between the conditions, the slope of the CNV was measured in the time window from 1600-1800 ms. This analysis was performed on signals from five groups of four electrodes, overlying left and right premotor, central parietal, and left and right occipitotemporal regions. These five groups of electrodes cover the maxima in the CNV distribution. For the short deviant a rising slope was found, whereas for the long deviant there was a down going slope, yielding a main effect of (preceding) SOA ($F(1,9)=5.20$, $p<0.05$). The effect was solely due to the modulation measured at left and right premotor regions, as demonstrated by a significant interaction of SOA by Area ($F(1,9)=9.99$, $p<0.05$) and post-hoc tests. For the left and right premotor region post-hoc t-tests yielded a significant difference in the slope of short and long deviant CNVs ($t(9)=3.14$, $p=0.012$, and $t(9)=3.34$, $p=0.009$, respectively). For the parietal and occipito-temporal locations, t-tests yielded t values <1.25, with p values >0.24. For the left and right premotor region, the difference between the CNVs was also quantified in terms of the CNV peak latency, determined in a search window between 1500 and 1850 ms. The peak latency was found to be significantly earlier for the CNV in the long deviant condition ($F(1,9)=8.06$, $p<0.05$). Together, these findings indicate that temporal deviance is registered in slow brain potential time course over lateral premotor areas. In combination with the results in the previous section, the findings demonstrate the operation of an interval timing process that creates a window of temporal attention with boundaries before and after the expected event.

2.3.2.3. Effects of SOA on oscillatory activity

Changes in oscillatory activity were evaluated from time-frequency representations, computed between 2-50 Hz for each channel over the entire duration of short and long SOAs (Figure 2.4).

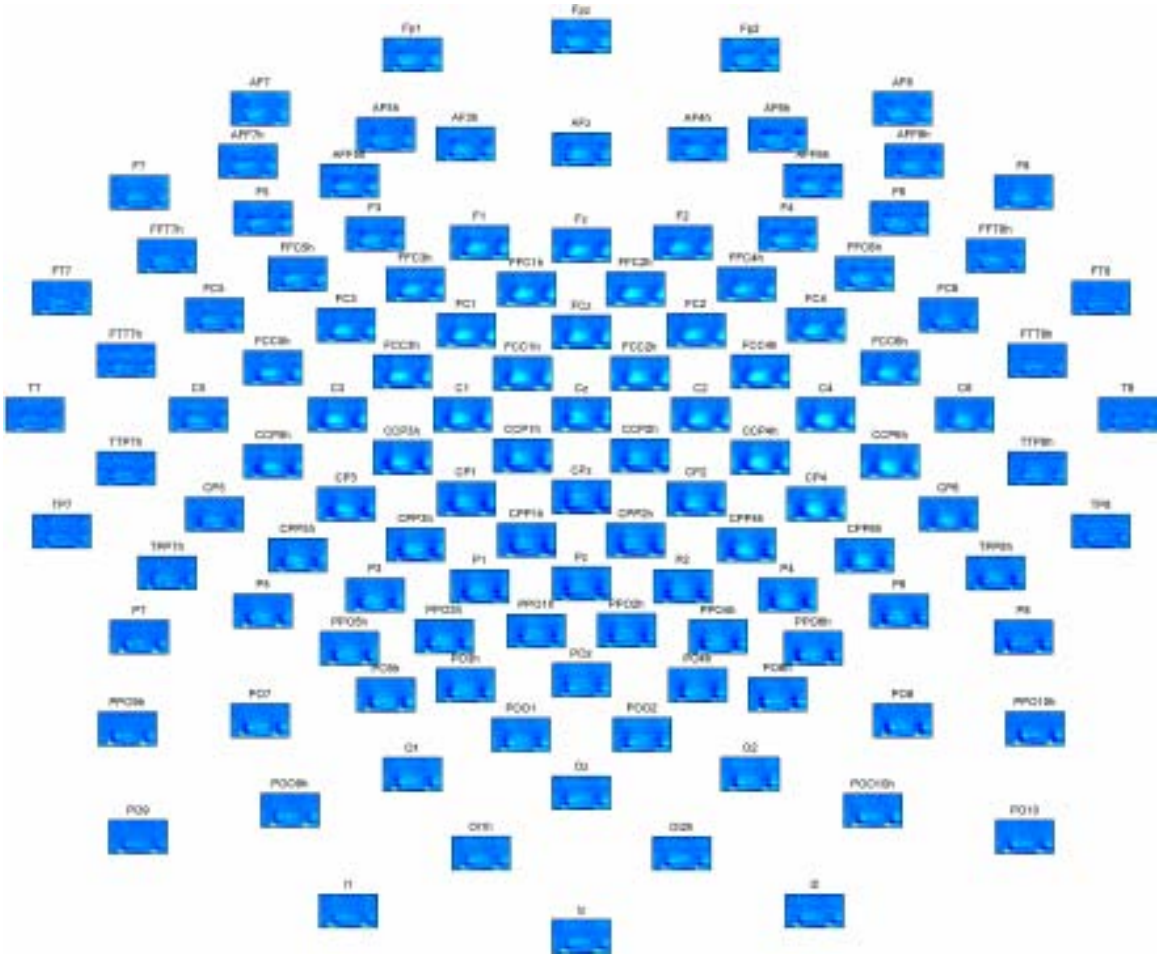

Figure 2.9: Time frequency plots (average data) of the long SOA, left hand condition for a 3500 ms time interval, starting 500 ms before stimulus onset. Frequency spans from 2 to 50 Hz. The top part of the figure corresponds to the anterior part of the brain. Beta ERS (in bright blue colour) demonstrated higher amplitude over bilateral sensorimotor region in a time-window of 850-1150 ms post stimulus onset.

This analysis revealed that the beta-band activity was modulated in a similar manner in all four conditions. The modulation was more pronounced over bilateral sensorimotor cortex. More specifically beta power demonstrated a decrease (i.e. ERD) right after stimulus onset, immediately followed by an increase, which reached maximum amplitude in a window of 850-1150 ms post stimulus for both SOA conditions (Figure 2.5).

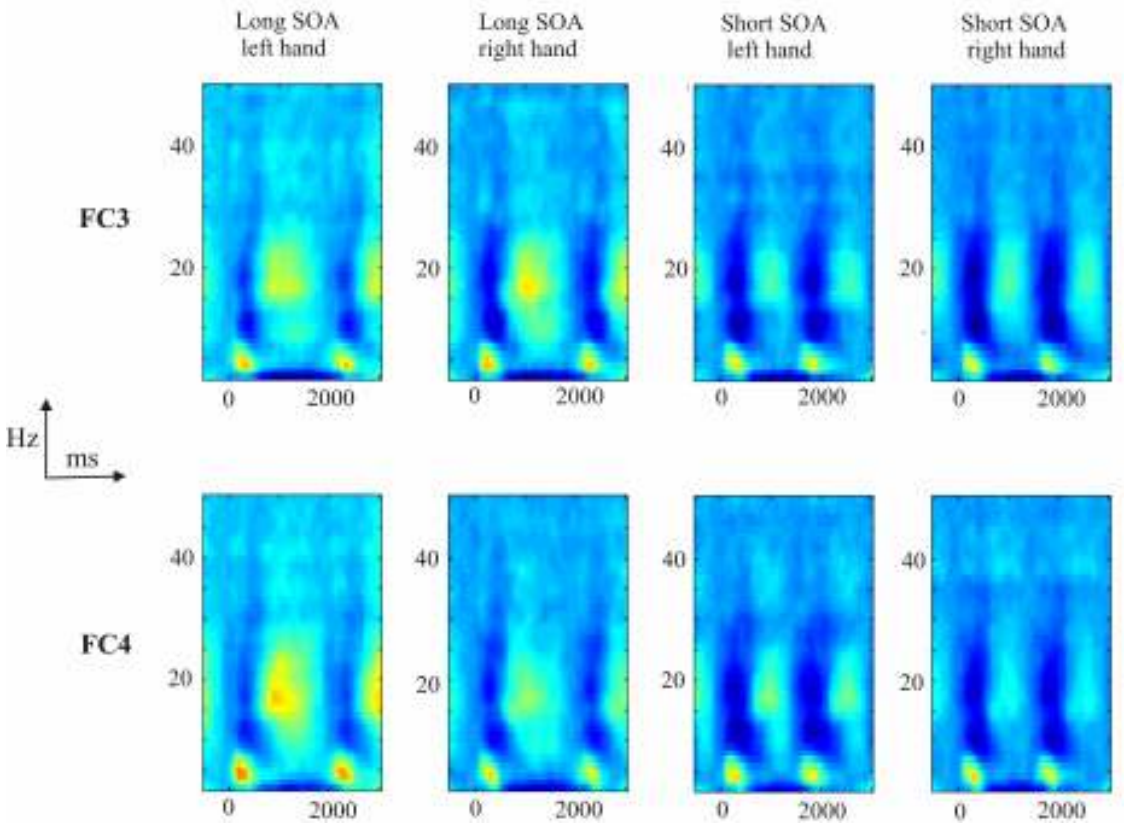

Figure 2.10: Time frequency plots (average data) for all four conditions for electrode sites FC3 and FC4. ERD is represented in deep blue colour and ERS in bright yellow/red colours.

Initial analyses of beta-modulation in relevant clusters of electrodes demonstrated differences in time course between the short and long SOA conditions. We defined two ROIs (regions of interest) by pooling the activities of five adjacent electrodes in each cortical hemisphere: (C1, C3, FC1, FC3 and FCC3h) and (C2, C4, FC2, FC4, FCC4h) for the left and the right hemisphere respectively. The frequency range was 14-24 Hz (where the modulation of beta band oscillations was stronger, see Figures 2.4 and 2.5) and the time windows 850-1150 ms and 1150-1450 ms post stimulus onset. In addition, by limiting the analysis in the 14-24 Hz band instead of the whole beta band (13-30 Hz), we avoided overlaps with task-induced modulations in the alpha and the gamma band. Analyses were performed using a four-way ANOVA with factors SOA, Epoch, Hemisphere, and Hand. The analysis showed a main effect of SOA ($F(1,9)=25.38$, $p=0.001$), due to a stronger ERS for the long SOA condition. The beta ERS peaked in the 850-1150 time window; beta power started to decline again in the subsequent time window, yielding a main effect of Epoch ($F(1,9)=15.13$, $p<0.05$). Importantly, this decline was steeper for the short SOA condition, resulting in an interaction of SOA by Epoch ($F(1,9)=29.29$, $p<0.001$). Beta ERS was stronger over the hemisphere contralateral to the response hand; however the interaction between Hand and Hemisphere failed to reach statistical significance ($F(1,9)=4.16$, $p=0.07$).

To capture both time course and localization of the beta activity modulation we applied a beamformer analysis to beta band activity in the same frequency range (i.e. 14-24 Hz and time windows (i.e. 850-1150 ms and 1150-1450 ms). The beta ERS effect was localized to bilateral motor cortex centered around Talairach-Tournoux coordinates $X=\pm30$, $Y=-16$, $Z=56$ (Figure 2.6).

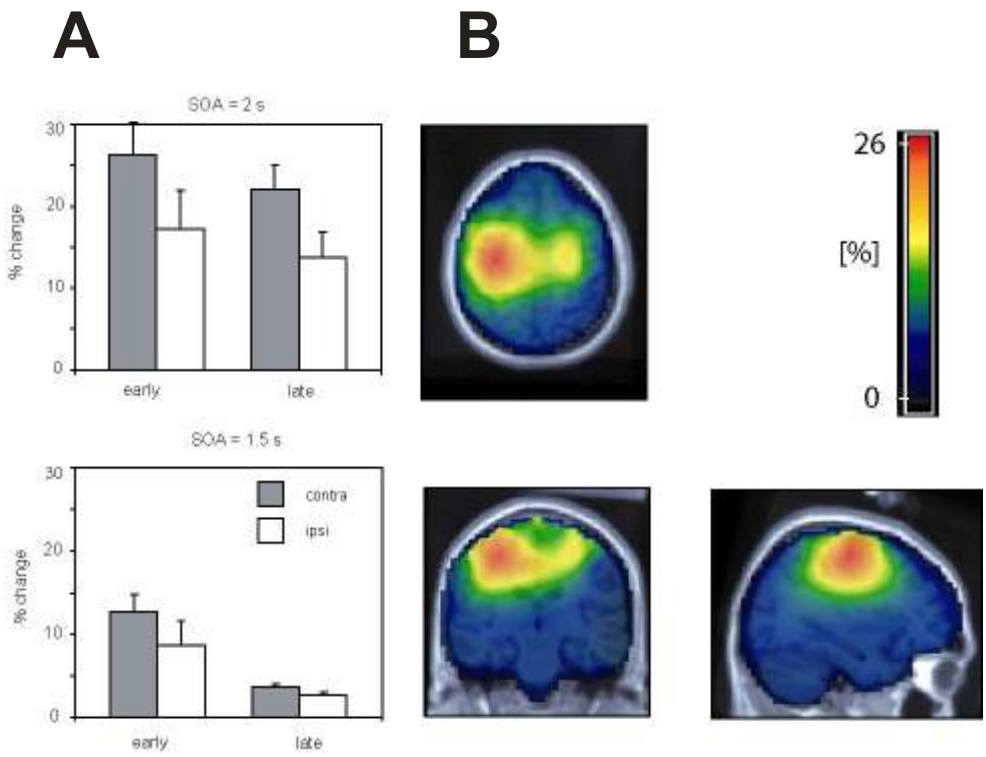

Figure 2.6: Beta band (14-24 Hz) modulation in precentral cortex. (A) Beta power change relative to baseline in time windows of 850-1150 ms (early) and 1150-1450 ms (late). (B) Grand average beamformer estimate of the beta power change in the long SOA condition with right hand responding (window 850-1150 ms) is shown. Error bars indicate SEM.

Analyses across conditions were performed on ROIs centered around the above coordinates, using a four-way ANOVA with factors SOA, Epoch, Hemisphere, and Hand. The analysis showed a main effect of SOA ($F(1,9)=27.43$, $P<0.001$), due to a stronger ERS for the long SOA condition. Similarly to the analysis at source level, the beta power peaked in the early time window and declined again in the subsequent time window, yielding a main effect of Epoch ($F(1,9)=7.84$, $p<0.05$). The decline was steeper for the short SOA condition, resulting in an interaction of SOA by Epoch ($F(1,9)=21.75$,

p<0.001). Beta ERS was stronger over the hemisphere contralateral to the response hand and contrary to the previous analysis, the interaction between Hand and Hemisphere was statistically significant ($F(1,9)=16.49$, $P<0.01$)).

The increase and subsequent decrease of beta power represent post-movement beta synchronization and preparatory desynchronization. The adjustment in the time course of the preparatory desynchronization reflects temporal preparation. The lateralization of this effect to the hemisphere contralateral to movement indicates that the preparation is much closer to the movement execution level than the symmetrical timing effects represented in the CNV.

2.3.2.4. Effects of timing perturbations on oscillatory activity

Given the small number of trials with deviant SOA, changes in oscillatory activity could not be analyzed with beamformer source reconstruction. Time-frequency representations were computed between 2-50 Hz as for the standard SOAs. Event-related changes in oscillatory activity were found only in the alpha band and are here represented by means of TSE waveforms (see Methods). Because the long and short deviant SOAs were of the same duration (1.75 s), any difference in EEG activity between them can be attributed to the temporal preparation conditioned by the preceding standard SOAs of 1.5 s or 2.0 s.

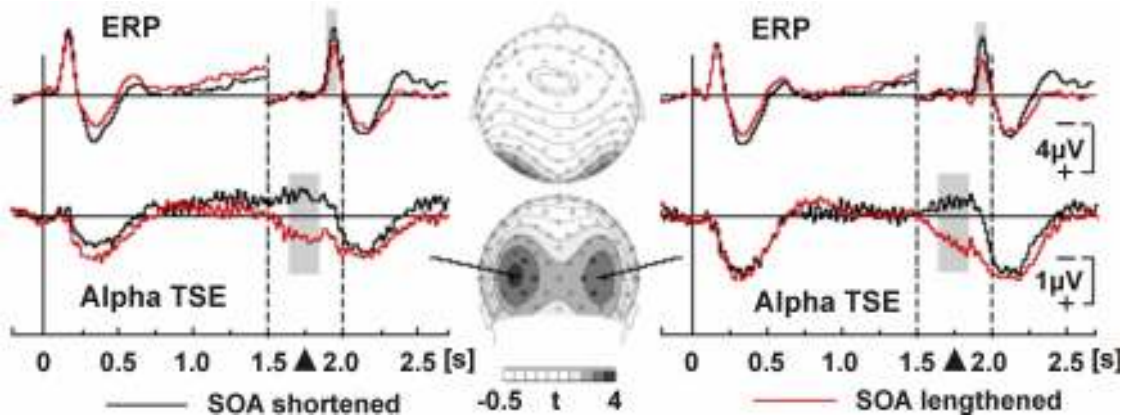

Figure 2.7: Modulation of visual evoked potentials and alpha activity. The TSE traces represent the temporal evolution of alpha activity during the deviant final SOAs of 1750 ms (time indicated by arrowhead). Alpha activity decreases sharply at 1500 ms i.e. the time of the expected stimulus in the short SOA condition. Alpha activity continues unchanged when the stimulus is expected at 2000 ms. The difference is quantified between 1650 and 1850 ms (grey bar) and represented in a t-map showing a distribution over the occipital scalp(uncorrected, two-tailed t-test). The four grey shades represent t-values between 2.2-4.0 (critical t-value for $p < 0.05$: 2.26). The stimulus in the long deviant condition occurring later than anticipated evoked a visual response of reduced amplitude, as illustrated in the ERP traces from four pooled electrodes. For better visualisation, the visual-evoked responses are displayed and quantified relative to a baseline between 1500-1750 ms.

The time-varying magnitude of activity in the alpha band (8-12 Hz) is illustrated in Figure 2.7 with TSE traces from the lengthened SOA condition superimposed on those of the shortened SOA condition. The former condition shows a sharp reduction of alpha activity at the time that participants expected the arrival of a stimulus (1.5 s). Comparison against the short deviant condition in a statistical parametric map shows that the

reduction in alpha activity is localized over the occipital scalp. The effect was further evaluated from two sets of four pooled electrodes overlying the left and right occiput in a time window of 1.65 to 1.85 s. An ANOVA with factors Hemisphere and Deviance demonstrated a significant difference between short and long deviants ($F(1,9)=10.22$, $p=0.011$), without hemispheric asymmetry.

Although alpha EEG activity is suppressed by visual stimulation, suppression in the absence of stimulation must be caused by internal timing, possibly reflecting a temporal attention mechanism. The possibility was supported by an attenuated visual-evoked response to the delayed stimulus (see Discussion). This response was smaller than the response to the immediately preceding stimulus at standard SOA ($F(1,9)=8.55$, $p=0.017$) as well as smaller than the response to short deviants ($F(1,9)=9.09$, $p=0.015$) (Figure 2.7).

2.3.2.5. Source characterization

To ascertain the presumed origin of the bilateral frontal maxima of the CNV in the lateral premotor cortex, we performed source analysis using a distributed multiple source modeling approach implemented in BESA. For each individual subject, conditions were pooled by aligning short and long SOA conditions at stimulus onset. These individual datasets were then combined in a grand average across subjects. The computed minimum norm current image of distributed activity on the smoothed cortical surface reproduced the bilateral frontal maxima of the scalp distribution. Like the scalp distribution, the

minimum norm current image showed a stable distribution over the 500 ms interval preceding the reaction stimulus (Figure 2.8). The centers of the source maxima were located at Talairach-Tournoux coordinates x=-46, y=-3, z=53 for the left frontal maximum and at x=43, y=-6, z=55 for the right frontal maximum. These locations are in the anterior zone of the precentral cortex corresponding with premotor cortex (Talairach and Tournoux, 1988).

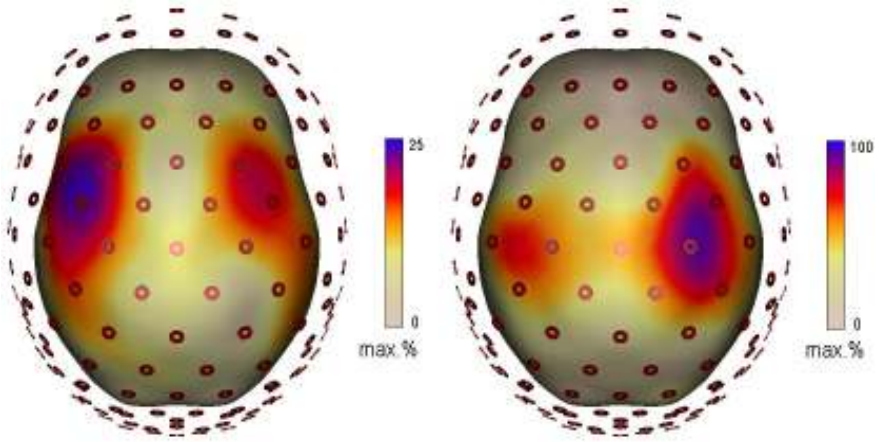

Figure 2.8: Minimum norm current estimates of the CNV (left) and movement-related activity (right). The current estimate for the CNV refers to a time point 200 ms before the reaction stimulus. The movement related sources were estimated at peak latency 40 ms before the button press. The source locations of the movement-related activity served as landmarks for verification of the origin of the frontal CNV maxima. The movement-related activity was higher than the CNV-related activity, hence different activity scales were used for presenting the results.

To lend additional credibility to the above analysis, we used movement-related EEG activity as a landmark for the hand motor cortex. For this purpose, the continuous EEG records were resegmented time-locked to the participants' motor responses and averaged across conditions, separately for left and right hand button presses. Finally, the left hand averages were subtracted from right hand averages in order to isolate movement-related from overlapping stimulus-related activity. Because of left-hemisphere motor dominance and consequent left hemisphere involvement in left hand movement (Kim et al. 1993), this subtraction shows stronger right than left motor cortex activation (Figure 2.8). The activation maxima were at x=-36, y=-25, z=59 in the left and at x=35, y=-22, z=58 in the right hemisphere. These maxima are in the posterior zone of the precentral cortex corresponding with the primary motor cortex (Talairach and Tournoux, 1988). The accurate localization of movement-related EEG potentials to the hand motor cortex provides support for the frontal CNV maxima originating in the premotor cortex.

The z-coordinates of the premotor cortex activation foci correspond with the dorsal rather than the ventral premotor cortex (cf. Schubotz and von Cramon, 2001a). Although the discussion below focuses on timing aspects of lateral premotor cortex revealed by the CNV, it is noteworthy that activation of the dorsal premotor cortex would also be expected on other features of the task. Both conditional motor tasks and visuospatial information processing invoke the dorsal premotor cortex (Halsband and Passingham, 1985; Toni et al., 1999; Schubotz and von Cramon, 2003).

2.4. Discussion

2.4.1. Slow brain potentials and implicit timing

Time intervals are represented in the brain either in explicit or in implicit fashion. In the former case, timing directly guides performance; in the latter case, timing is not a crucial factor for optimal task performance. Contrary to the view that only the execution of continuous rather than discrete movements involves implicit timing processes (Zelaznik et al., 2002), the present study provides evidence that the presentation of fixed period stimuli conditions temporal expectation in an implicit manner. Temporal conditioning as a result from presentation of successive periodic stimuli has been demonstrated in EEG recordings in the form of omitted stimulus potentials. These potentials are evoked in the absence of an anticipated stimulus in an ongoing sequence of regular sensory events (Sutton et al., 1967, auditory stimuli); (Klinke et al., 1968, vibratory stimuli); (Barlow, 1969, visual stimuli)). However, the drawback of this method is that it does not provide information about the evolving process of temporal encoding. This requisite is addressed in the present investigation by studying the development of the Contingent Negative Variation during the interstimulus time intervals.

Our results demonstrate that the CNV developed between periodically presented stimuli and reached a fixed amplitude approximately at the end of the entrained interval. The amplitude was the same irrespective of the duration of the interstimulus interval. This was achieved by adjustment of the CNV slope, which was steeper in the short SOA condition. CNV slope has been reported to vary inversely with interval duration (Pfeuty et al., 2005), where participants had to compare a test duration against a standard

memorized one. CNV amplitude increases with longer intervals have been reported in an earlier study (Macar et al., 1999); however this behaviour was related to participants' estimates and it probably reflected memory-based subjective timing (Macar et al., 2002). In the present study, the termination of the CNV rising was not signalled by the presentation of the following stimulus. In the long deviant SOA (i.e. when the last stimulus was presented 250 ms later than expected), the CNV peaked around the time of the expected stimulus and then dropped in amplitude before the arrival of the belated stimulus. Similar CNV behaviour has been observed by Macar and Vidal (2003) when a test duration was judged against a memorized one. In that study, the rise of the CNV slope was terminated at the end of the memorized interval, despite the current stimulus being longer. These results indicate that the CNV does not just reflect motor readiness, but expresses the estimated duration of a stored interval. This study additionally shows that duration encoding does not necessitate explicit memory processes but it can be realized by exposition and reaction to periodically presented stimuli (i.e. conditioning).

Whereas the time course as well the peak latency and amplitude of the CNV in our implicit timing task are in accordance with CNV behaviour in explicit timing tasks, the scalp topographies demonstrate a distinct difference. It is widely accepted, that in implicit timing tasks, the median fronto-central cortex, in particular the supplementary motor area (SMA) plays an important role in time processing, which is reflected in the CNV timing properties. This notion has been corroborated by imaging studies where increased preSMA/SMA has been consistently found in timing tasks (Schubotz and von Cramon, 2001b; Macar et al., 2002; Ferrandez et al., 2003; Coull et al., 2004; Pouthas et al., 2005). In addition, the preSMA/SMA is linked to the striatum forming a pathway,

which is a likely candidate for the neural substrate of an internal timer/ pulse accumulator mechanism (Meck, 1996).

In the present implicit timing investigation, the foci of activation, responsible for the generation of the CNV, were overlying the left and right lateral premotor regions. Scalp topographical maps did not show SMA activation, neither did the localization method using minimum norm current estimates. Neuronal activity caused by anticipation of a predictable event has been recorded from the macaque lateral premotor cortex by Mauritz and Wise (1986). Rosahl and Knight (1995) examined patients with dorsolateral prefrontal cortex lesions and found a significant reduction in the later part of CNV (~1000 ms prior to the second stimulus), which is typically associated with motor readiness. The lateral premotor cortex gets activated in continuous interval and sequence-encoding tasks (Schubotz and von Cramon, 2001b) and tasks requiring discrimination of deviant elements inserted into a periodic sequence of sensory events (Schubotz et al., 2000). The activation is not related to motor output and it is even present in motor imagery (Schubotz and von Cramon, 2001b). In all cases lateral premotor activation was accompanied by SMA activation. Such activation may reflect the encoding of sensory and perceptual events providing a reference platform for mnemonic representational functions associated with motor planning or imaging. In agreement to this, Pouthas et al. (2005) found lateral premotor activation directly associated with duration estimation, which was attributed to the active maintenance of temporal parameters. For example, the lateral premotor cortex ability to interface sensory events with temporally structured movements could be evoked for performing an action synchronized to rhythmic events.

Accordingly, activation of the lateral premotor cortex has been found during externally paced and conditional tapping (Jäncke et al., 2000; Kurata et al., 2000; Chen et al., 2006).

Schubotz and von Cramon (2003) summarized the timing function of the lateral premotor cortex as both extraction and prediction of sequential/temporal information. In this framework, the fixed CNV peak amplitude approximately at the end of the entrained interval likely reflects motor prediction. The drop in amplitude in the long deviant SOA, right after the time of the (absent) expected stimulus can be regarded as the capacity of the lateral premotor cortex for extracting sequential/temporal information.

In our experiment, an additional focus of activation was found over the centroparietal region, which contributed to the generation of the CNV. The origins of this activation could be located in the left and the right superior parietal cortex or in the medial parietal cortex. Bilateral superior parietal lobe activation has been found in a externally paced/continuation rhythmic task (Jantzen et al., 2005). Activation of the superior as well as the inferior parietal cortex has been demonstrated by (Rao et al., 2001) in a time perception paradigm. Parietal activation associated with time perception has been more frequently found in the inferior parietal cortex in a variety of paradigms (Coull et al., 2004; Harrington et al., 2004; Rubia and Smith, 2004); lesion studies offered further credibility to this notion (Harrington et al., 1998; Schubotz et al., 2004).

2.4.2. Modulation of oscillatory activity and implicit timing

An impostant finding in our study, with respect to the modulation of the cortical oscillatory rhythms, was the adjustment of the time course of the activity in the beta band to the duration of the SOAs. Beta band activity demonstrated a decrease (ERD) after stimulus onset, immediately followed by a rapid increase (ERS), which reached peak amplitude in a time window 850-1150 ms post stimulus for both short and long SOA. After reaching a peak value, beta activity progressively returned to the baseline value. The drop in amplitude in the following time window (i.e. 1150-1450 ms post stimulus) was greater in the short SOA condition. This resulted from preparation for a motor response to the subsequent (expected) stimulus; the stricter time requirements in the short SOA condition dictated a faster and greater beta activity decrease. Anticipatory decrease in the beta band prior to self-paced or stimulus-guided movements is common ground in motor tasks (Bastiaansen et al., 1999; Cassim et al., 2000; Filipovic et al., 2001; Alegre et al., 2003a, 2006; Gómez et al., 2004b). Beta ERD manifestation does not require motor execution (Leocani et al., 2001) or proprioceptive afferents (Pfurtscheller and Neuper, 1997; Pfurtscheller et al., 1999a) and it is related to cognitive processes (e.g. timing) needed for response selection (Kaiser et al., 2001).

After movement offset, beta activity increased and gradually exceeded premovement levels. Time-frequency analysis at the scalp level showed that this increase (termed ERS or beta rebound) originated from bilateral precentral areas. Source localization, by means of beamformer analysis, confirmed the validity of this finding; furthermore it demonstrated that beta ERS was stronger in the contralateral to the

response hemisphere. Our results are in agreement with numerous EEG and MEG studies, which identified the sources of beta ERS in the precentral cortex (Salmelin et al., 1995; Pfurtscheller et al., 1996; Van Burik and Pfurtscheller, 1999b; Neuper and Pfurtscheller, 2001b; Jurkiewicz et al., 2006). Parkes et al. (2006), using combined EEG-fMRI analysis, has recently argued in favour of a post-central beta ERS generator. However, several methodological issues raised by this study (see Jurkiewicz et al., 2006) render this view rather improbable.

The analysis of the event-related spectral perturbations in the alpha band revealed a difference between the short and the long deviant conditions. Whereas in the short deviant SOA the alpha activity decreased after stimulus presentation, in the long deviant SOA the decrease started at the time of the expected but absent stimulus. Oscillation in the alpha band is commonly known as the "cortical idling rhythm"; the reduction of alpha activity in a specific brain area is regarded as an indication of cortical excitation. Consequently, the presentation of a visual stimulus causes an amplitude drop of the alpha activity in the occipital cortex. However, occipital alpha ERD can also result by the allocation of visuospatial attention in the absence of visual stimulation (Thut et al., 2006). In our experiment, occipital alpha ERD also occurred in the absence of visual stimuli (long deviant SOA). Moreover, since the stimuli were always presented at the centre of the screen, no orientation of visuospatial attention was required. We perceive the decrease in alpha activity at the time of the expected stimulus as an expression of allocation of temporal attention, a notion which is supported by the attenuated visual response to the delayed stimulus.

It has been shown that stimuli are processed faster and more accurately when they occur at an attended point in space, irrespective of their modality (Posner, 1980; Mondor and Zatorre, 1995; Spence et al., 2000). In addition, Lange and Röder (2006) have recently shown that perceptual processing is facilitated for temporally attended stimuli across all modalities. Earlier work suggested that attention to a stimulus is only related to changes in later ERP components (e.g. Miniussi et al., 1999). However, recent studies have proven that allocation of spatial or temporal attention enhances early perceptual processes as well (Lange et al., 2003; Doherty et al., 2005; Lange and Röder, 2006). Importantly, it has been demonstrated that temporal attention has a beneficial effect on unconscious perceptual processing (Naccache et al., 2002; Kiefer and Brendel, 2006). Our results are in line with these findings, indicating that implicitly-paced phasic allocation of temporal attention facilitates early perceptual processes.

Noticeably, in our experiment, the amplitude of the visual response was attenuated in the deviant SOAs compared to preceding normal ones, while the activity remained well below baseline. This finding could suggest that the reduction of alpha activity terminates a state of heightened sensitivity to expected stimulation. However, the suppression of alpha oscillations is typically associated with active stimulus processing (Fries et al., 2001; Van der Togt et al., 2006; Bauer et al., 2006) and it also enhances visual detection and discrimination performance (Hanslmayr et al., 2005). Consequently, it is also possible that the reduction of alpha activity initiated a facilitation of sensory processing. In this case, we would ecpect that the alpha ERD would be accompanied by enhanced visual responses; however, we observed the opposite effect. It has been demonstrated though that the amplitude of early ERPs is influenced by the pre-stimulus

phase of the alpha rhythm (Barry et al., 2004). Additionally, there is growing evidence that early ERPs are at least partly generated by phase locking of the ongoing alpha oscillations (Klimesch et al., 2004, 2006; Hanslmayr et al., 2005, 2007; Gruber et al., 2005). These more transient effects are critical determinants of evoked-response amplitude (Makeig et al., 2002), hence it is possible that they are responsible for the seemingly discrepant results in our study.

2.5. General Discussion

It is common ground in human and animal studies that the preparatory interval (PI) effect modulates reaction times. The PI effect refers to information and decision making processes inherent in a task, which take place during a certain time interval before stimulus onset. Moreover, interval timing processes are strongly interconnected with reaction time processes (for a review, MacDonald and Meck, 2004) as well, which comes into agreement with the reaction time measures in the present experiment. Our findings provide neurophysiological evidence for the operation of interval timing mechanisms that are recruited in an implicit manner by the temporally regular structure of the task. Related mechanisms of time-based sensory and motor anticipation may underlie timing in predictive motor control.

The time course and the amplitude adjustment of the CNV, which developed between successive stimuli in our implicit timing task, were similar to the ones recorded in explicit timing tasks. However, contrary to explicit timing tasks, we did not find

significant SMA activation (Macar et al., 1999; Pfeuty et al., 2005); instead, the CNV originated form sources in lateral premotor structures. This divergence suggests that depending on the nature of the task, different cortical areas are engaged in order to implement similar timing mechanisms. These distinct cortical areas possibly produce the same effects by virtue of participating in a flexible, general-purpose timing mechanism, which is generated by a cortical-thalamic-striatal network (Buhusi and Meck, 2005). Movement preparation due to the expected presentation on an imperative stimulus is reflected in the modulation of the beta activity. The sources of this modulation were located in the bilateral precentral/motor areas, with a contralateral to the responding hand predominance. Anticipatory activity was also demonstrated in the sensory domains in the modulation of occipital alpha activity and the attenuated visual evoked response. Our data do no establish whether motor and sensory anticipation are coordinated by a central timekeeper. Therefore, it remains possible that implicit timing emerges from a distributed state-dependent neural network, intrinsically capable for temporal information processing (Buonomano, 2000; Mauk and Buonomano, 2004; Karmarkar and Buonomano, 2007).

Pfeuty et al. (2005) pointed out the similarity between the time course of the CNV and the temporal profile of delay-period sustained activity of neuronal subpopulations located in frontal (Niki and Watanabe, 1979; Akkal et al., 2004), parietal (Leon and Shadlen, 2003) and thalamic (Komura et al., 2001) areas. The temporal characteristics of this activity fit the model of "climbing neuronal activity", (Komura et al., 2001; Durstewitz, 2003, 2004; Reutimann et al., 2004), which postulates the existence of neuronal subsets whose activity, during a delay period, depends on the presentation of an anticipated imperative stimulus rather than the presented cue. Similar to the CNV, the

slope of this activity inversely correlates with the interval length and reaches maximal amplitude at the time of the expected stimulus. If the expected stimulus (or reward) does not occur at the predicted time point, both CNV and climbing activity rapidly decrease in amplitude (Komura et al., 2001; Durstewitz, 2003). Striatal activity is also known to demonstrate a "ramplike" sustained pattern before an anticipated event (Apicella et al., 1992; Schultz et al., 1992). In addition, a recent study in rats showed that ramplike activity recorded by striatal spiny neurons peaked at the end of two different time intervals (Matell et al., 2003); temporal encoding was reflected in the neural firing rate which was adjusted to interval duration.

Importantly, models of neuronal climbing activity suggest the existence of a cortical timer/pulse accumulator mechanism, through which time encoding occurs incidentally rather than being intrinsic to a task (Reutimann et al., 2004). This is also an important feature of reward-based learning models using the "error in reward prediction", which is the difference between the predicted and actual time of reward occurrence (Hollerman and Schultz, 1998; Durstewitz, 2003). In these models, midbrain dopamine neurons fit the role of neurons producing an error signal, thus shaping the climbing profile of anticipatory prediction signals (Suri and Schultz, 2001). Based on such a role of midbrain dopamine neurons, the basal ganglia are in a position to influence implicit timing in a wide range of different behaviours.

Chapter 3

Maintaining grip: anticipatory and reactive EEG responses to load perturbations.

* A modified version of this chapter has been published as:

Kourtis D, Kwok HF, Roach N, Wing AM, Praamstra P (2008) Maintaining grip: anticipatory and reactive EEG responses to load perturbations. J Neurophysiol 99:545-553.

Abstract

Previous behavioral work has shown the existence of both anticipatory and reactive grip force responses to predictable load perturbations, but how the brain implements anticipatory control remains unclear. Here, we recorded EEG while participants were subjected to predictable and unpredictable external load perturbations. Participants used precision grip to maintain the position of an object perturbed by square wave load force pulses. The force pulse onsets were either distributed randomly over an interval 700-4300 ms (unpredictable condition) or they were periodic with interval 2000 ms (predictable condition). Preparation for the predictable load perturbation was manifested in slow preparatory brain potentials and in EMG and force signals recorded concurrently. Preparation modulated the long-latency reflex elicited by load perturbations, with a higher amplitude reflex response for unpredictable compared to predictable perturbations. Importantly, this modulation was also reflected in the amplitude of motor cortex potentials just preceding the long-latency reflex and in the amplitude of sensory-evoked responses. Together, these results support a transcortical pathway for the cutaneously mediated long-latency reflex and a central modulation of the reflex grip force response.

3.1. Introduction

Precision grip can be defined as the hand posture where an object is held between the flexed and axially rotated fingers and the abducted and medially rotated thumb (Napier, 1956). In the case of a small object, the precision grip consists of the thumb opposed to one of the fingers, usually the index finger. The requisite is to maintain a secure as well as a promptly adjustable grip with minimum energy cost.

The grip force, which is applied perpendicularly to the object, resists the gravitational and other external load forces in order to avoid slipping. Its magnitude depends on the load forces' magnitudes, tangential to the surface and inversely on the friction coefficient of the object's surface. It has been observed that the grip force is always higher than the minimum required force for the performance of a task. The ratio of the excess grip force over the minimum grip force to avoid slipping is called safety margin (Westling and Johansson, 1984). The safety margin is relatively small in order to avoid unnecessary use of energy, which will lead to fatigue. Application of a low level of grip force also allows the detection of small perturbations and the assessment of the object's properties (e.g. weight and texture of the object), which make its manipulation easier.

The development of the grip force precedes the load force in self-initiated movements (Johansson and Westling, 1984), when transporting an object vertically or horizontally in a continuous manner (Westling and Johansson, 1984; Flanagan and Wing, 1995), when performing point-to-point arm movements (Flanagan and Wing, 1993) and also when the movement produces load torques (Wing and Lederman, 1998). However, it

should be noted that Blakemore et al. (1998) showed that self-generation of a movement is not sufficient for prediction unless "the sensory feedback is consistent with a single object". Additionally, the grip force starts rising before the load force in the case of an external load with a predictable time course (Serrien et al., 1999; Turrell et al., 1999; Kwok and Wing, 2006) or with a known time of impact (Johansson and Westling, 1988b). Such results provide evidence for the existence of an internal forward model in motor control (Wing et al., 1997; Flanagan et al., 2003).

The cortical substrates of predictive motor control are not yet clear; however it is believed that several brain areas play a significant role, such as the cerebellum, the basal ganglia, sensorimotor and parietal cortices (Witney et al., 2004). It seems likely that the cerebellum is involved in rapid, possibly unaware predictions while the parietal lobe gets activated in cognitive prediction (for a review, Blakemore and Sirigu, 2003 and also Sirigu et al., 2004). The importance of the cerebellum in predictive force coupling has been highlighted in PET studies; activation was also found in the caudate nucleus and frontal association regions (e.g. anterior cingulate cortex), bilaterally in the primary motor cortex, the caudal supplementary motor cortex, the ipsilateral to the hand used inferior parietal cortex and the contralateral primary sensory, dorso-caudal premotor and cingulated motor cortices (Kinoshita et al., 2000; Takasawa et al., 2003; Boecker et al., 2005). Further evidence for the significance of the cerebellar and parietal regions in predictive force coupling was provided by fMRI studies (Ehrsson et al., 2003; Kawato et al., 2003; Milner and Hinder, 2006). In addition, frontal areas such as the ipsilateral inferior gyrus pars opercularis (area 44) and the rostral cingulated motor area are activated possibly in combination with parietal areas such as the parietal operculum and

the supramarginal gyrus, forming a "fronto-parietal" network, which seems to play an important role in object manipulation (Ehrsson et al., 2001; Schmitz et al., 2005). Several of these structures have been examined with single-cell recordings in monkeys where the primates resisted predictable and unpredictable load force perturbations. Although this has yielded evidence for preparatory activity in the cerebellar cortex and the nucleus interpositus (Dugas and Smith, 1992; Monzee and Smith, 2004), there is a surprising lack of evidence for preparatory activity in primary motor, lateral premotor, supplementary motor and cingulate motor areas (Picard and Smith, 1992; Cadoret and Smith, 1997; Boudreau et al., 2001) to explain preparatory grip force modulation.

The anticipatory modulation of the grip force prior to a predictable load perturbation is not reflected solely in the pre-load period, but also in the post-load response. The application of a load when holding an object in a precision grip produces a sudden rise in grip force, which precedes the voluntary response. This reflex response may comprise at least two discernible EMG components. The first one, termed the short latency reflex has an onset latency of about 30 ms (for the hand muscles) and it is of subcortical origin (Johansson et al., 1994). The second one, termed the long latency reflex, has an onset latency of 60-70 ms (for the hand muscles) and it is widely accepted that its generation involves a transcortical loop (e.g. Palmer and Ashby, 1992; Johansson et al., 1994; Macefield and Johansson, 1994).

MacKinnon et al. (2000) identified the cortical generator of the long latency reflex, which was elicited by rapid angular wrist displacements. The authors reported the activation of a dipole source with a peak latency of 54 ms (named the N54-P54

component), whose location and orientation was compatible with a source generated in the anterior banks of the central sulcus (i.e. motor cortex), contralaterally to the task-involved hand. However, they didn't find any task-dependent modulation of the N54-P54 dipole source (although it was present in the EMG), which lead them to the suggestion that the long-latency reflex is not modulated in the cortical level.

In our experiment, we examined whether, when holding an object in precision grip, the grip force rises prior to a periodical external load, which is produced by a robotic arm and also studied the neural correlates of the grip force modulation prior and post load onset. In our paradigm the produced long-latency reflex is most likely mediated by fast cutaneous afferents (Macefield and Johansson, 1994; Corden et al., 2000). We used high density EEG recordings to address the cortical basis of predictive and reactive grip force control in response to load perturbations. Furthermore, presence or absence of phasic motor cortical activity at an appropriate latency for the generation of the long latency reflex should be informative regarding the possibility of a transcortical reflex pathway. Finally, an interaction between preparatory and reactive EEG effects in grip force control might shed light on the integration of predictive control and afferent information.

3.2. Methods

3.2.1. Participants

Eight males and six females (age: 28 ± 8 years old) took part in the experiment. Twelve were right-handed and none of them had any history of hand or wrist injuries or diseases or any mental, cognitive, and other neurological disorder. All the participants provided their informed consent after full explanation of the study.

3.2.2. Task and Apparatus

Participants sat comfortably on a chair in a quiet, normally illuminated room with their right wrist resting on a support and their eyes directed towards a fixation cross placed 1m in front of them at the eye-level in order to reduce eye movements. A manipulandum attached to a lightweight robot (PHANTOM1.5, Sensable Technologies, R.I.) was held between the right thumb and index finger (Figure 3.1). Two load cells (Nano 17, ATI Industrial Automation, Apex, N.C.), which measured forces and torques in six directions, were attached to each side of the object. The signals were sampled at a rate of 500Hz. The task consisted of four experimental blocks preceded by a training one, where the participants were instructed and supervised upon the performance of the trial. The four experimental blocks consisted of two blocks of randomly-timed square wave force pulses and two blocks of regularly-timed square wave force pulses with the order of the blocks alternating between participants. Each block consisted of 5 to 10 trials of 60-second duration. Prior to the start of the experiment, the participants were instructed to hold the object without letting it slip while the manipulandum delivered downward 1 N force

pulses of 500 ms duration. For the regular trial series, the inter-pulse interval was 2 seconds and for the random trials, the intervals between pulses were uniformly randomized between 0.7 to 4.3 seconds. In the random condition, only those force pulses that followed the previous force pulse by ≥ 2.5 seconds were used for analysis (in order to avoid overlapping of pre- and post-load phenomena) yielding a total number of trials of 249, compared to 240 for the regular condition. The participants were allowed to rest as long as they wished between blocks to avoid fatigue.

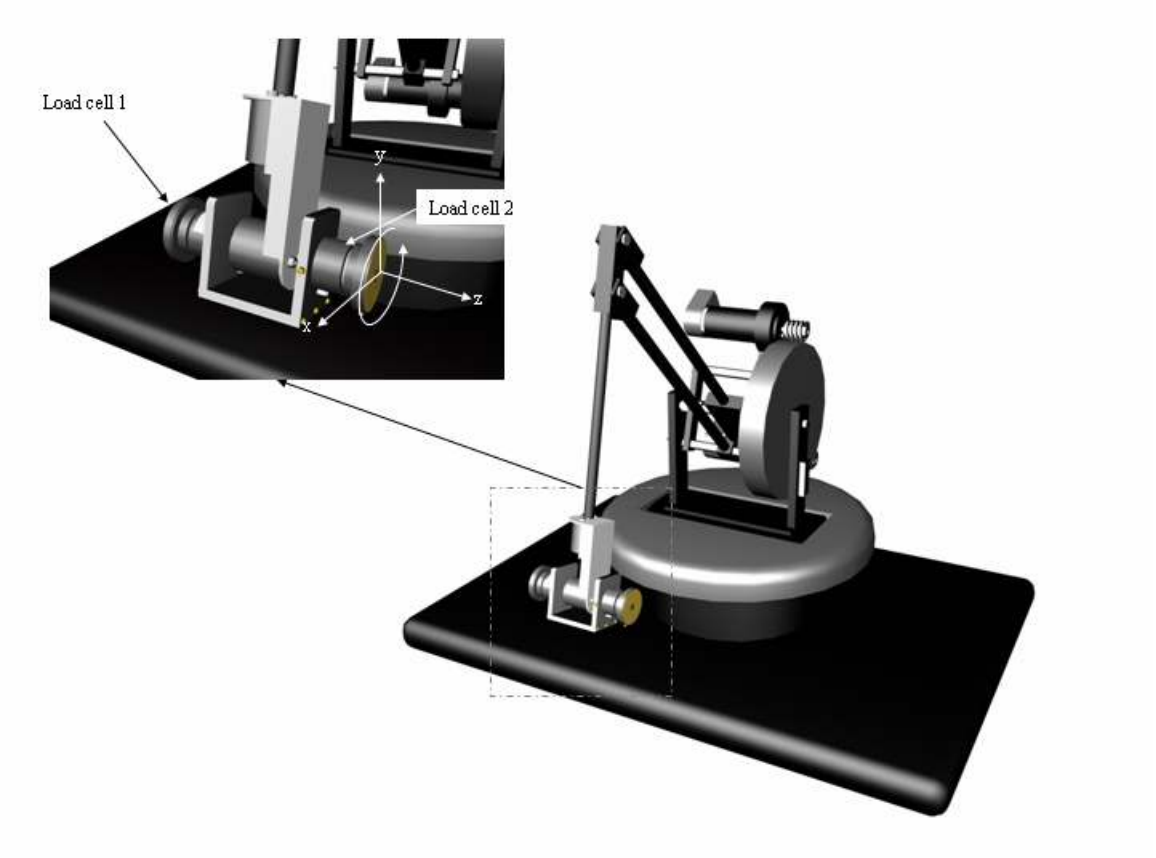

Figure 3.1: Diagram of the robotic arm with the manipulandum and the convention for x, y, and z-axes (on the top-left figure) for forces.

3.2.3. EEG and EMG data acquisition

EEG was recorded continuously with Ag/AgCl electrodes from 128 scalp electrodes. The electrodes were placed according to the 10-5 extension of the International 10-20 electrode system (American Electroencephalographic Society, 1994; Oostenveld and Praamstra, 2001) using a carefully positioned nylon cap. Vertical eye movements were monitored using two electro-oculography (EOG) electrodes placed right below the eye pupil, whereas horizontal eye movements were monitored using the nearest to the eyes cap electrodes (FFT9h/FFT10h). Horizontal ones were controlled using the nearest to the eyes cap electrodes.

EMG was recorded from the first dorsal interosseous muscle (FDI) and from the abductor pollicis brevis (APB), using 2 pairs of Ag/AgCl electrodes.

The EEG, EOG and EMG were sampled at 1024 Hz and amplified (DC-256 Hz) by the BioSemi Active-Two amplifier (Biosemi, Amsterdam, Netherlands). A trigger was used to send the onset time of the square wave force pulses from the PHANTOM robot to the EEG data acquisition system.

3.2.4. Data Analysis

The grip force was derived using the following formula:

$$F_G(t) = \frac{|F_{z1}(t)| + |F_{z2}(t)|}{2} \qquad (3)$$

where $F_{z1}(t)$ and $F_{z2}(t)$ are the forces along the z-axis (Figure 3.1) measured by load cell 1 and load cell 2 respectively. The load force was defined as the total measured force orthogonal to the grip force and was given by:

$$F_L(t) = \sqrt{F_{x1}^2(t) + F_{y1}^2(t)} + \sqrt{F_{x2}^2(t) + F_{y2}^2(t)} \qquad (4)$$

where the subscripts *x1*, *y1*, *x2*, *y2* refer to the forces in the x- and y- axis, measured by the two load cells.

The EMG and EEG data were first filtered. The continuous EMG recordings were high-pass filtered at 20 Hz using a 4th order Butterworth zero phase-shift filter. The EEG was low-pass filtered at 70 Hz using a 4th order Butterworth zero phase-shift filter. All data (Force, EMG and EEG) were then segmented. Each segment started 1500 ms before the external load trigger and ended 500 ms afterwards. Artifact processing was performed in the following way. In the case of artifacts in EMG or force signal, the relevant segment was removed for all three measures (force, EMG, EEG). The number of trials thus removed was (mean ± SD) 1.1 ± 3.4 % in the regular condition and 0.7 ± 2.7 % in the random condition. Since the number of trials affected by an artifact in one (or more) of the EEG channels was far greater (24.5 ± 9.8 % for the regular and 23.5 ± 10.5 % for the random condition), but equal for both conditions, the corresponding force and EMG signals of those trials were retained. Further details of the analyses of the force, EMG and EEG data are presented below.

3.2.5. Force Data

In order to verify accurate load force timing relative to the load pulses generated by the Phantom robot, a thresholding algorithm was applied to measure load force onset. The section from 500 ms to 250 ms prior to the trigger of each segment was used as the baseline. A force of two standard deviations above the mean baseline load force was used as the threshold. The time when the load force first exceeded this threshold after the trigger was regarded as the onset time. The mean delays were 5.4 ± 0.2 ms and 4.7 ± 0.2 ms (mean ± SE), respectively, for the random and regular conditions.

For the grip force data, the average force from the first 250 ms of each segment was taken as the baseline and subtracted from the force data. The baseline-corrected segments were then averaged separately for each participant and condition. Preparatory force adjustment was assessed on the basis of the mean amplitude from -500 to 0 ms before the load perturbation. A paired t-test was used to compare the response in the two conditions. For comparison of the grip force responses following the load perturbation, the grip force was re-baselined to the mean amplitude in the 100 ms before the load force onset.

3.2.6. EMG Data

The continuous EMG recordings were rectified and checked for artifacts due to electrode movement in a semi-automatic artifact rejection procedure. For the analysis of EMG preparatory activity the baseline was defined as the mean amplitude in the window from

1000 to 800 ms before load onset, whereas for the long latency reflex the baseline adopted was from 100 ms to 0 ms before load onset. The onset latency and peak latency of the long latency reflex were detected automatically within selected time windows, and checked visually. The amplitude was measured at peak latency.

3.2.7. ERP analysis

EEG data processing used BrainVision Analyser software (BrainProducts GmbH, Gilching, Germany). Artefact rejection was performed semi-automatically on the basis of artefact thresholds determined individually. For each participant, the segments from each condition (random or regular) were then averaged and baseline corrected. For analysis of the pre-load activity, the baseline was defined as the period from 1400 ms to 1200 ms before load onset, whereas for the post-load activity the baseline was defined as the period from 200 ms to 0 ms before load onset. All EEG signals were analyzed with respect to the common average reference.

EEG preparatory activity was analyzed by pooling the slow brain potential amplitude values of a set of neighbouring electrodes over the midline central scalp area, identified on the basis of the scalp distribution of the grand average data. Phasic sensorimotor cortex activity immediately preceding the long-latency reflex was analyzed on the basis of a composite amplitude measure. This measure was computed as the sum of the (absolute) amplitude values taken at the negative and positive polarity maxima of this activity's dipolar field distribution, i.e., electrodes F1 and CP3, respectively. The

same activity was also analyzed by means of a dipole source analysis (see below). Differences between the regular and the random condition were evaluated by means of paired t-tests.

3.2.8. Time – Frequency analysis

The continuous EEG data were originally divided into segments from 2000 ms before till 500 ms after load onset. The rationale behind this was that although we wouldn't be able to fully observe the evolution of post load ERD (Event Related Desynchronization) and ERS (Event Related Synchronization) with this particular segmentation, we would get a more clear idea of the period where the activity remains stable (baseline period). By carefully inspecting the data we decided, taking into account the limitations imposed by the short interstimulus interval, to consider as baseline the period from 900 to 700 ms before load onset.

Following that, we performed a new segmentation from 1000 ms before till 2000 ms after load onset. Using the above mentioned baseline we analyzed the pre and post load percentile changes of cortical oscillatory activity in relation to the baseline activity, which was set by default to have the value of 100.

The modulation of the beta activity was studied in the 18-24 Hz subband, which is typically associated with motor control. The data were then bandpass filtered (Butterworth zero phase-shift filters (24 dB/octave)), rectified and averaged according to the temporal spectral evolution method (TSE) (Salmelin and Hari, 1994b).

Preload ERD was analyzed by pooling the values of four neighbouring electrodes (C3, CCP3h, CP3 and FCC3h) over the contrallateral sensorimotor area. The selection of these electrodes was based on the scalp distribution of the grand average data. The same procedure was followed in order to examine the post load beta ERS in the time intervals from 1000 ms to 1500 ms post load onset. In addition, one sample t-tests were used to assess the statistical significance of the beta ERD/ERS components.

3.2.9. Dipole Source analysis

Dipole source analysis was performed using the Brain Electrical Source Analysis software (BESA V. 5.1.2, MEGIS software GmbH, Gräfelfing, Germany). The analysis was applied in order to quantify the sensorimotor cortex activity immediately preceding the long latency reflex. This activity was represented in a phasic component peaking at 58 ms after load onset, designated as N58-P58 by analogy to the N54-P54 identified by MacKinnon et al. (2000), as a cortical contribution to the generation of the long latency reflex. The advantage of quantifying this component in terms of dipole strength is that this approach takes the entire scalp distribution into account. The analysis used the standard BESA volume conductor head model, i.e. a four-shell ellipsoidal head model (head radius 85 mm; brain conductivity 0.33 mho/m; scalp thickness 7 mm and conductivity 0.33 mho/m; Bone thickness 7 mm and conductivity 0.0042 mho/m; cerebrospinal fluid thickness 1 mm and conductivity 1 mho/m (Rush and Driscoll, 1968, in Oostendorp et al., 2000). The N58-P58 component was modeled for each participant by one regional source, which was subsequently reduced to a single dipole source. No

constraints were imposed on the dipole in terms of location of origin and orientation. Dipole source location was specified in Talairach-Tournoux coordinates, whereas the orientation in theta and phi angles, which correspond to the azimuth and the polar angle respectively (Figure 3.2).

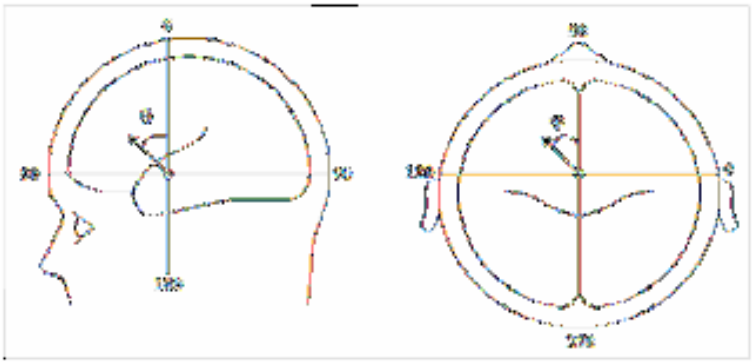

Figure 3.2: Polar coordinates system

The strategy of modeling the isolated N58-P58 component as opposed to a spatio-temporal modeling procedure for the entire epoch (cf. MacKinnon et al., 2000), was chosen because this approach is less susceptible to bias by subjective decisions on modeling parameters. The potential drawback of not accounting for overlapping activity from other sources was deemed less relevant, since single dipole models explained the data with reasonable goodness of fit. This was not the case, however, in three participants (participants no. 4, 7 and 12) in whom the N58-P58 in the regular condition could not be adequately modeled with a single dipole, due to temporal preparation effects in the form of enhanced alpha/mu activity over the right hemisphere. A principled approach of modeling this activity on the basis of narrow (8-12 Hz) band pass filtered data, with a single dipole, was only successful in two out of the three participants. As a simple

alternative approach, applicable in each of the three participants, the activity was modeled by fitting an additional single dipole simultaneously with the N58-P58 dipole. This dipole assumed a location in parietal/sensorimotor cortex of the right hemisphere. For comparisons between regular and random condition, this dipole was also added to the model for the random condition in these three participants.

The validity of the single dipole solution for each participant was assessed by three criteria: i) the difference between the activity "generated" by the dipole source and the one recorded on the scalp (which is expressed as the ratio of the total variance (power) of the data: residual variance) should be minimal during the fitting interval, ii) the dipole source location and orientation should be in agreement with the scalp topography, and iii) the solution should be neurophysiologically plausible. The dipole onset and peak latencies, along with the dipole moment magnitudes were quantified for both the regular and the random condition and compared using a paired t-test.

3.3. Results

3.3.1. Force Data

The mean (± SE) baseline grip force was 6.4 ± 1.6 N and 6.5 ± 1.6 N for the random and regular conditions respectively. The difference was not statistically significant. The grand average grip force response to the random and regular load force perturbations are shown in Figure 3.3, along with the EMG and EEG responses. In the random condition, the preload grand average grip force did not vary significantly from the baseline and the grip

force increased after the trigger. In contrast, in the regular condition, there was a slow rise in the grip force preceding the trigger and the grip force rose further after the trigger. The average grip force in the 500 ms interval before the load force onset was higher in the regular condition compared to the random condition (0.089 ± 0.027 vs. 0.030 ± 0.012 N; $t(13)=-3.39$, $p=0.0049$).

To analyze the grip force response following the load perturbations, the signals were re-baselined to the mean amplitude in the 100 ms before the load force onset. Thus aligned, the grip force response in the random condition was higher than in the regular condition, with waveforms separating around the latency of 100 ms. The amplitudes were compared in 25 ms overlapping 50 ms time windows from 100 to 300 ms. Results showed that the difference between the random and regular condition started to become statistically significant at 150 ms. In the time window between 175 and 225 ms (around the grip force peak), the baseline-corrected grip force was 0.68 ± 0.06 N and 0.56 ± 0.04 N ($t(13) = 2.80$, $p = 0.015$), respectively, in the random and regular condition.

In both conditions, the rise in the grip force after the trigger coincided with the load force change and preceded the EMG response. We believe that this was due to mechanical factors. We conducted a test by replacing the human fingers in the experimental setting with a pair of rubber pads and delivered a downward load force using the PHANTOM. We found an immediate increase in the measured z-axis force, directly corresponding to the change in load force applied to the x and y axes. This could be due to mechanical cross-talk between the different axes of the 6-DOF transducers. The early grip force rise does not affect the evaluation of EEG and EMG data.

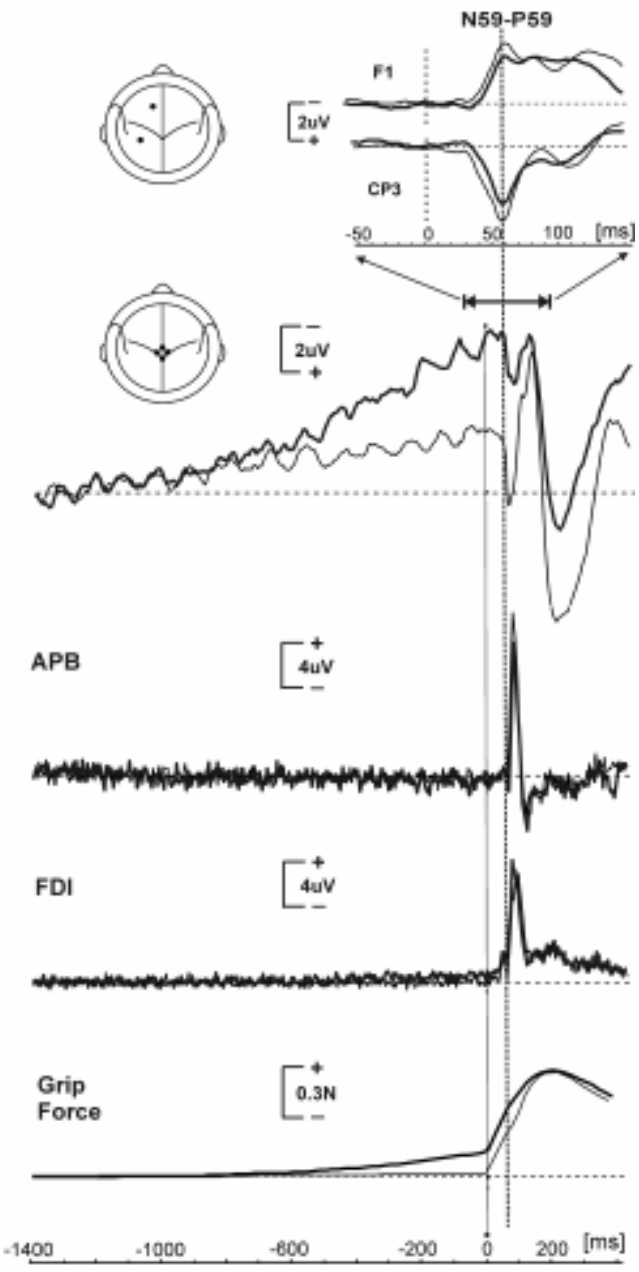

Figure 3.3: Grand Average (from top to bottom) the N58-P58 sensorimotor cortex activity, preparatory slow brain potentials at central midline electrodes (Cz, CPz, CCP1h, and CCP2h), EMG activity from m. abductor pollicis brevis (APB) and m. interosseous dorsalis I (FDI), and grip force recording. The horizontal dashed lines represent the baseline. Thin lines refer to the random condition and bold lines to the regular condition. The solid and the dashed vertical lines represent load onset and N58-P58 peak latency (i.e. 58 ms post load onset), respectively.

The slope of the grip force change in the 500 ms interval before the load force onset in the random and regular conditions are shown in Table 3.1. All participants showed steeper slope of the grip force rise in the regular condition compared to the random condition ($t(13)=-5.22$, $p<0.001$).

Table 3.1: Grip force data -The slope of the grip force change (in Ns^{-1}) measured in the 500 ms interval before the load force onset in the random and regular conditions

Participant	Slope of the grip force (Ns^{-1})	
	Random	Regular
1	0.086	0.412
2	0.018	0.032
3	0.045	0.263
4	0.023	0.371
5	-0.050	0.205
6	0.071	0.268
7	0.019	0.100
8	-0.002	0.253
9	-0.009	0.032
10	0.114	0.650
11	0.023	0.212
12	-0.067	0.476
13	-0.016	0.137
14	0.001	0.069
Mean ± SEM	0.018 ± 0.013	0.249 ± 0.048

3.3.2. EMG analysis

As shown in the grand average EMG data (Figure 3.4), there was a difference in the preload activity in the FDI muscle between random and regular conditions, with an anticipatory increase of EMG activity for the regular condition, which started around 500 ms and became more evident around 300 ms before load onset. On the contrary, no

preparatory activity was recorded from the APB in either condition (Table 3.2). Consequently, the analysis regarding the preparatory EMG activity was restricted to the FDI muscle.

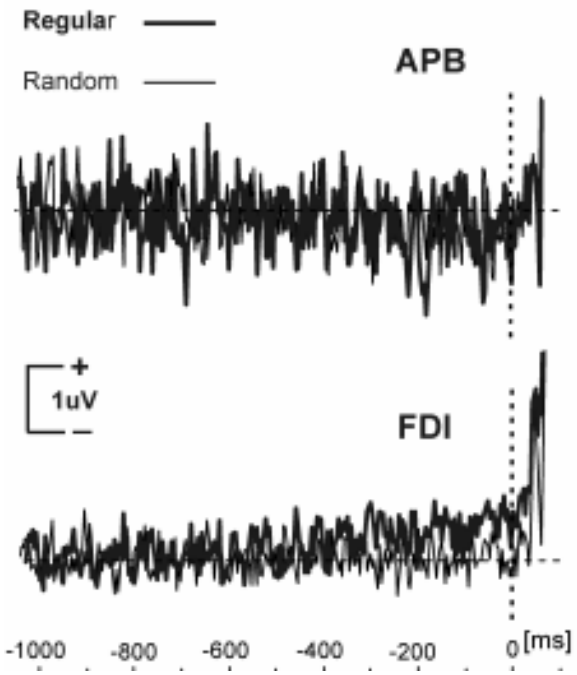

Figure 3.4: Grand average EMG traces from 1000ms before the load onset to 50ms after the load onset recorded over the APB and the FDI muscles. The vertical axis (time 0) represents load onset. The horizontal dashed line represents baseline. There is an increase in EMG activity, recorded over the FDI muscle, in the regular condition (thick line) starting around 500 ms before load onset.

The mean (preparatory) activity from 500 to 0 ms before load onset was higher in the regular condition (Table 3.2); the difference was assessed by means of a paired t-test and it was found to be statistically significant ($t(13)=-3.273$, $p=0.006$).

Table 3.2: Average preparatory EMG activity from 500 ms till 0 ms before load onset recorded from the APB and the FDI muscles for the random and the regular condition.

Participants	APB		FDI	
	Regular Preparatory Activity (μV)	Random Preparatory Activity (μV)	Regular Preparatory Activity (μV)	Random Preparatory Activity (μV)
1	-3.4	-1.59	0.30	0.05
2	-0.07	0.01	0.07	-0.01
3	-0.03	0.34	1.74	0.47
4	0.05	0.01	0.08	0.01
5	0.36	-0.14	0.67	-0.28
6	-0.77	0.01	0.22	0.06
7	-0.31	0.23	0.02	-0.02
8	0.33	0.01	0.42	-0.12
9	0.02	-1.25	0.33	-0.01
10	0.32	-0.05	0.96	0.02
11	-0.08	-0.07	0.02	0.07
12	0.02	0.05	0.10	-0.04
13	-0.07	-0.04	-0.06	0.04
14	-0.05	-0.41	0.75	0.18
Mean	-0.26	-0.21	0.40	0.03
SEM	0.25	0.15	0.13	0.04

The post load onset EMG waveforms revealed an EMG component in both muscles, whose latency was too long to be a spinal reflex (~30-35 ms e.g. Macefield and Johansson, 2003) and too short to be a voluntary response (rarely less than 100 ms, e.g. Pascual-Leone et al., 1992). Specifically, for the ABP muscle the onset latency was (mean ± SE) 63.5 ± 0.9 ms and 63.7 ± 0.7 for the regular and the random condition, respectively, while the peak latency was 84.8 ± 1.3 ms and 85.5 ± 1.9 ms for the regular and the random condition, respectively. The amplitude was 12.0 ± 3.1 μV and 16.0 ± 4.5 μV for the regular and the random condition, respectively. For the FDI muscle the onset latency was 63.9 ± 1.4 ms and 63.7 ± 1.1 for the regular and the random condition

respectively, while the peak latency was 86.7 ± 2.1 ms and 89.1 ± 2.4 ms for the regular and the random condition respectively. The amplitude was 10.5 ± 4.4 μV and 9.9 ± 4.7 μV for the regular and the random condition, respectively (Table 3.3). This response presumably reflects the long latency reflex (LLR), whose generation may involve a transcortical loop.

Table 3.3: LLR parameters for the random and the regular condition.

Participant	Abductor Pollicis Brevis		First Dorsal Interosseous	
	Random Condition	Regular Condition	Random Condition	Regular Condition
	LLR Peak Amplitude (μV)	LLR Peak Amplitude (μV)	LLR Peak Amplitude (μV)	LLR Peak Amplitude (μV)
1	49.1	29.4	5.4	3.5
2	4.1	3.8	5.7	4.2
3	6.6	12.7	16.7	20.5
4	10.1	2.5	12.4	5.8
5	18.0	12.8	9.0	7.5
6*	3.5	3.9	3.0	2.6
7	42.8	33.7	3.0	2.4
8	13.8	10.8	14.6	11.8
9	45.8	30.9	41.8	65.4
10	5.2	5.0	5.8	7.0
11	2.2	0.7	4.1	2.9
12	2.8	0.9	3.8	2.9
13*	3.5	2.0	3.3	2.3
14	17.6	19.4	10.0	8.7
Mean	16.0	12.0	9.9	10.5
SEM	4.5	3.2	2.7	4.4
* : Left-handed participants				

The magnitude of the LLR, recorded from the APB muscle, was higher in the random condition. This difference was evident in the grand average data (Figure 3.5) and, by means of a paired t-test, it was found to be statistically significant ($t(13) = 2.194$, $p = 0.047$). The magnitude of the LLR, recorded from the FDI muscle, was higher in the

random condition for eleven out of fourteen participants. However, this result was not present in the grand average data (Figure 3.5), mostly due to participant no 9, who showed an exceptionally high response, which was higher in the regular condition. Therefore, the difference in LLR magnitude was assessed by means of a non-parametric Sign test. This analysis showed a higher LLR magnitude in the random over the regular condition that nearly reached significance (p=0.057; two-tailed). Non-parametric evaluation of the LLR recorded from the APB yielded the same values (p=0.057; two-tailed).

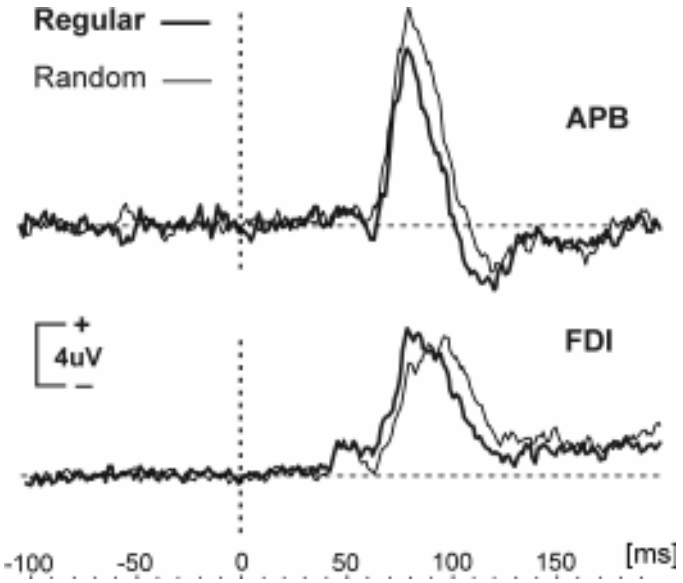

Figure 3.5: Grand average EMG traces recorded over the APB and the FDI muscles showing the long latency reflex (LLR) for both the random (thin line) and the regular condition (thick line). The vertical axis (time 0) represents load onset. The horizontal line represents baseline.

We also examined whether the modulation of the LLR magnitude was caused by modulation of the background EMG activity. Non-baseline corrected EMG data analysis showed the EMG activity in the time window between 100ms and 0 ms before load onset

was higher in the regular condition for the APB ($t(13) = -2.579$, $p = 0.023$) and the FDI ($t(13) = -2.948$, $p = 0.011$) muscles. This activity was positively correlated with the LLR magnitude recorded from the APB and the FDI muscles (Pearson's correlation test, $r = 0.903$, $p<0.001$ and $r = 0.657$, $p<0.001$, respectively).

3.3.3. ERP analysis

Waveforms of the grand average data, recorded over the mid sensorimotor area are shown in Figure 3.3 (second plot from the top). The waveforms represent the mean of electrodes Cz, CCP1h, CCP2h and CPz, the selection of which was based on the scalp distribution of the preparatory activity (see Figure 3.6). Preparatory cortical activity is represented in a slow brain potential of negative polarity, which starts at about 1000 ms before load onset and shows a clear differentiation between the two conditions around 750 ms before load onset.

The voltage map (Figure 3.6) shows focal activation over mid sensorimotor areas with a slight contralateral predominance. The latter becomes more evident in the CSD map (inherently sensitive to sources with radial orientation, Pernier et al., 1988), where the activation seems to be generated mainly by two distinct sources, most likely located in the primary motor cortex. The statistical parametric map of the difference between conditions shows that motor cortex activation is stronger in the regular condition, especially in the hemisphere contralateral to the response hand.

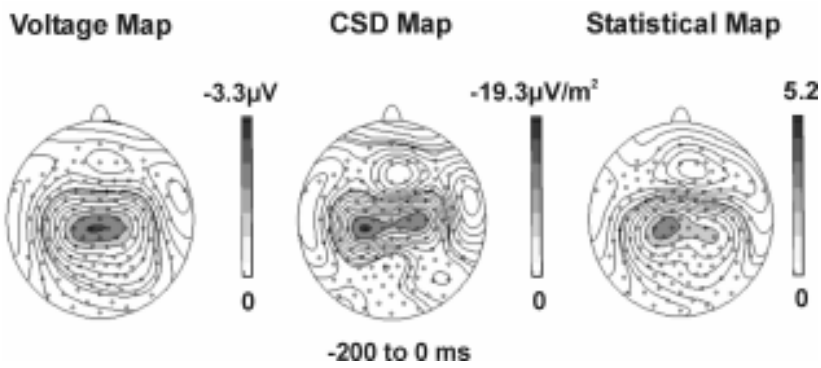

Figure 3.6: Scalp voltage distribution (left) and current source density distribution (middle) of the preparatory activity in the regular condition in the time window between 200 ms and 0 ms before load onset. Statistical parametric map (t-map) of the difference (right) between regular and random condition in the same time window (critical t-value for $p<0.05$: 2.16).

The mean amplitude from 500 ms to 0 ms before the load onset for both conditions, measured in the midline area of interest was (mean ± SE) -2.0 ± 0.4 μV and -0.7 ± 0.2 μV for the regular and the random condition, respectively (Table 3.4). Twelve out of fourteen participants showed higher (i.e. more negative) preparatory activity in the regular condition. Participant no14 showed no modulation and participant no 9 showed higher preparatory activity in the random condition. Despite the presence of these two participants, a paired t-test demonstrated a significance difference ($t(13) = 4.445$, $p=0.001$) between the two conditions.

Table 3.4: Mean amplitude of EEG preparatory activity recorded over mid sensorimotor areas (electrodes Cz, CPz, CCP1h and CCP2h) in the time window between 500 ms to 0 ms before load onset.

Participants	Mean Amplitude (μV)	
	Random Condition	Regular Condition
1	0.1	-1.8
2	-0.5	-1.2
3	-1.9	-3.9
4	-0.2	-1.6
5	-0.8	-1.3
6	-1.2	-4.0
7	-1.3	-2.2
8	-1.6	-4.6
9	-0.3	-0.1
10	-1.1	-3.7
11	0.05	-0.3
12	-0.4	-1.2
13	-1.0	-1.9
14	-0.1	-0.1
Mean	-0.7	-2.0
SEM	0.2	0.4

Analysis of the post-load EEG waveforms revealed a component of similar orientation and location as the N54-P54 component studied by MacKinnon et al. (2000), which they identified as the source of the descending corticospinal output of the LLR. In the present data, this component peaked at about 58 ms after load onset, thus termed N58-P58 component. The topographical maps (Figure 3.7) of the grand average data show that this component was generated by a tangential dipole source with the negative pole over the mid frontal areas and the positive one over the left parietal cortex. The amplitude of the N58-P58, measured as the sum of the negative peak maximum at F1 and the positive peak maximum at CP3, was significantly smaller in the regular compared to

the random condition (t(13)=5.826, P<0.001). To quantify the strength of motor cortex activation and to determine the location and orientation of its source we also performed a dipole source analysis, presented in the "Dipole Source Analysis" section.

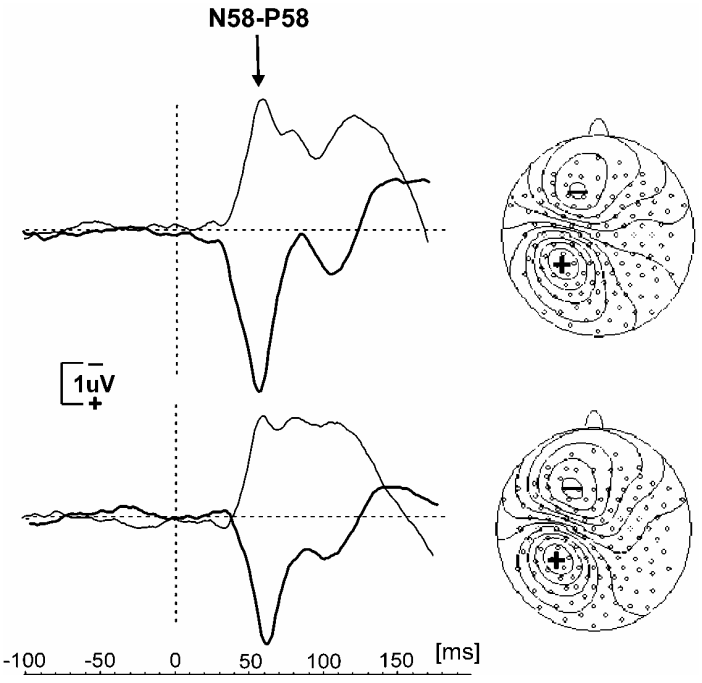

Figure 3.7: The N58-P58 component as represented in waveforms recorded from electrodes F1 (thick line) and CP3 (thin line) and in scalp topographies for the random (top) and the regular condition (bottom).

3.3.4. Time-Frequency analysis

A clear reduction of cortical oscillatory activity (ERD) prior to load onset in the beta band was evident only in the regular condition and started around 500 ms before load onset. The focus of the beta ERD was located over the left (contralateral to the movement) sensorimotor areas, most likely over the primary motor cortex (Figure 3.8).

The reduction in power recorded at the electrode sites C3, CP3, FCC3h and CCP3h in the time interval from 500 ms prior to till load onset, was statistically significant ($t(13) = -3.597$, $p = 0.005$) when compared to the baseline period. On the contrary, no significant beta ERD was observed in the random condition ($t(13) = -1.190$, $p = 0.255$). The statistical comparison (paired t-test) of the two conditions, showed that the amplitude of beta power was significantly lower in the regular condition ($t(13)=3.823$, $p=0.002$).

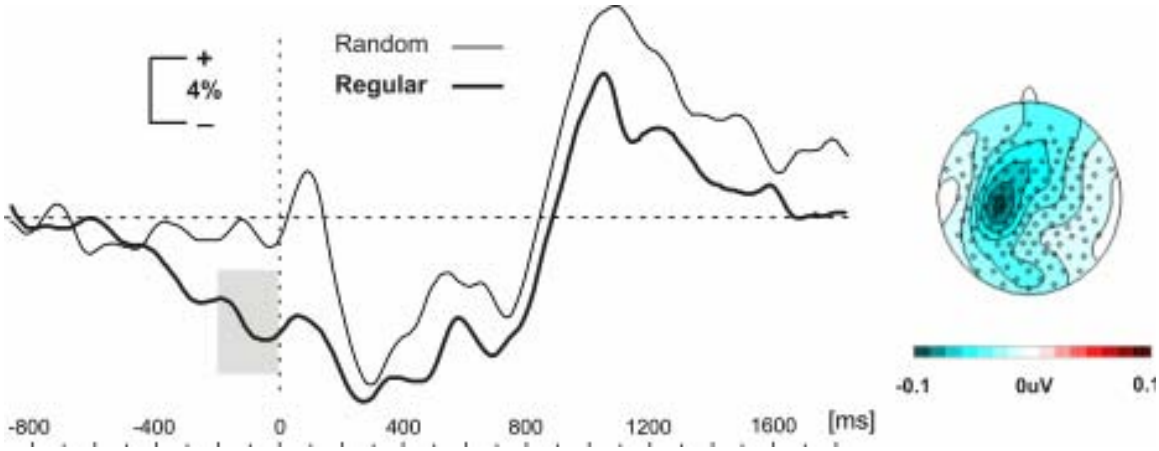

Figure 3.8: Modulation of cortical oscillatory activity in the beta frequency band (electrode C3) for the random (thin line) and the regular (thick line) condition and scalp topography of the pre-load ERD component for the time window between 200 ms and 0 ms (grey box) before load onset. The vertical dashed line indicates load onset.

An ERS component, stronger over the contralateral to the movement sensorimotor areas, was evident in both conditions starting around 900 ms after load onset (Figure 3.9). The same ROI (i.e. electrode sites C3, CP3, FCC3h and CCP3h) was selected for analysing the motor beta ERS; one sample t-tests revealed that the ERS amplitude from 1000 to 1500 ms post load onset was significantly higher compared to the baseline: ($t(13)= 4.353$, $p=0.001$) and ($t(13)=2.878$, $p=0.013$) for the random and the regular condition respectively. The statistical comparison (paired t-test) of the two conditions, showed that the amplitude of beta power was significantly higher in the random condition ($t(13)=3.587$, $p=0.003$).

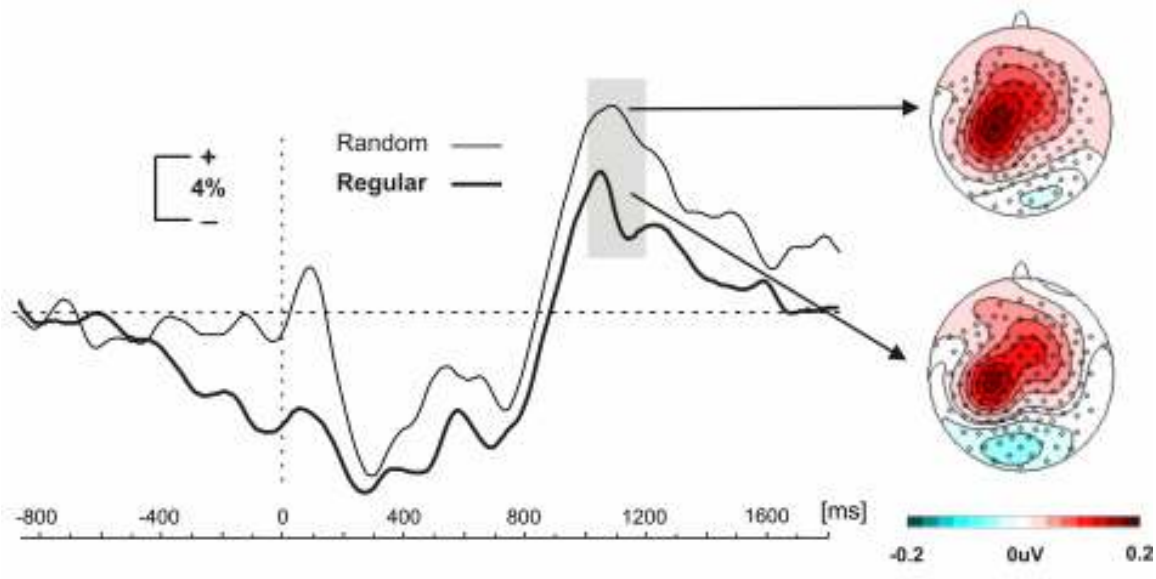

Figure 3.9: : Modulation of cortical oscillatory activity in the beta frequency band (electrode C3) for the random (thin line) and the regular (thick line) condition and scalp topography of the post-load ERS component for the time window between 1000 ms and 1200 ms (grey box) after load onset. The vertical dashed line indicates load onset.

3.3.5. Dipole Source analysis

The N58-P58 component was modeled in the individual participant data using a single dipole source, separately for the random and the regular condition. The dipole source models explained the recorded data with a residual variance always less than 26%. The (mean ± SE) residual variance was 12.2 ± 2.2 % for the regular condition and 8.3 ± 1.4 % for the random condition. For all the participants, the location and the orientation of the dipole were virtually identical for the random and the regular condition (Figure 3.10).

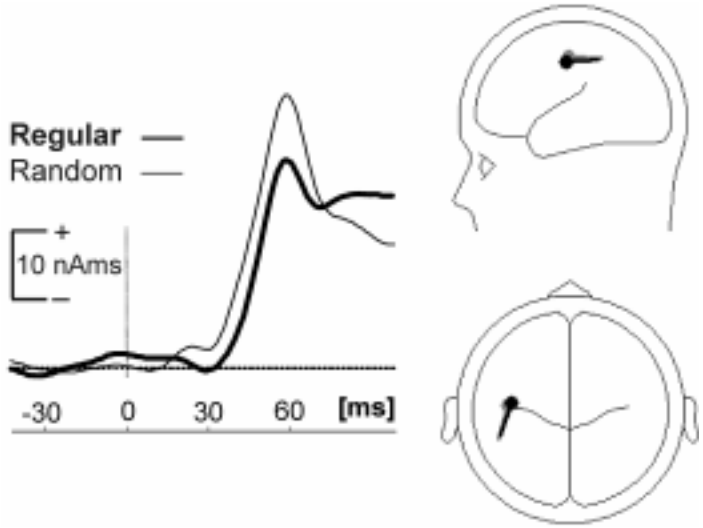

Figure 3.10: Dipole source waveforms and N58-P58 dipole source locations based on data from eleven of the fourteen participants and the average source waveforms.

The tangential orientation and frontal negative maximum of the source were compatible with a motor cortex generator in the anterior wall of the central sulcus. The azimuth and the polar angle defining the source orientation were $\theta=92 \pm 4^{o}$ and $\varphi=248 \pm$

4 ^{o} for the random condition and θ=91.5 ± 4 ^{o} and φ=253 ± 4 ^{o} for the regular condition. The Talairach-Tournoux coordinates (Talairach and Tournoux, 1988) correspond to a precentral generator location, both for the random (x=-38 ± 1, y=-15 ± 2, z=44 ± 2) and the regular condition (x=-39 ± 2, y=-16 ± 3, z=46 ± 3).

The onset and peak latencies of the source waveforms as well as the dipole source strength of eleven out of fourteen participants are presented in Table 3.5. There was no statistical difference between the two conditions in onset latency (t(10)=-0.575, p=0.578), nor in peak latency (t(10)=-1.843, p=0.095).

Table 3.5: N58-P58 parameters in dipole source waveforms.

Participant	Random Condition				Regular Condition			
	Onset latency (ms)	Peak latency (ms)	Peak amplitude (nAm)	Residual Variance (%)	Onset latency (ms)	Peak latency (ms)	Peak amplitude (nAm)	Residual Variance (%)
1	40.1	61.6	59.5	7.6	38.1	60.6	45.6	12.4
2	33.2	58.6	26.4	12.2	31.3	59.6	19.9	24.9
3	33.2	59.6	53.5	2.4	31.3	63.5	32.6	7.6
4	33.2	60.6	27.7	7.6	31.3	58.6	17.8	6.1
5	31.3	57.6	60.9	6.1	32.2	59.6	56.8	3.0
6*	31.3	57.6	62.2	5.5	30.3	58.6	50.3	4.3
7	26.4	46.9	32.0	6.9	29.3	49.8	13.4	25.6
8	34.2	59.6	43.5	15.0	33.2	58.6	39.3	14.3
9	45.9	56.7	47.7	13.0	44.9	56.7	69.2	6.9
10	32.2	60.6	59.4	3.5	38.1	60.6	44.4	6.5
11	35.2	61.6	64.9	3.0	36.2	61.6	54.5	3.3
12	33.2	60.6	20.6	5.8	39.1	63.5	6.3	17.0
13*	29.3	56.7	32.0	7.1	36.2	58.6	16.1	23.6
14	35.2	49.8	25.7	25.7	35.2	50.8	39.0	15.0
Mean	33.8	57.7	44.0	8.2	34.8	58.6	36.1	12.2
SEM	1.2	1.2	4.3	1.4	1.2	1.1	5.1	2.2
* : Left-handed participants								

The source strength was higher in the random condition ($t(13)=2.499$, $p=0.027$). Note that this result corresponds with the analysis based on scalp amplitude values taken at F1 and CP3, except for a lower significance level in the dipole source analysis. Also noteworthy, in both analysis approaches participants no. 9 and 14, who showed a reversed and absent preparatory EEG modulation, respectively, were found to have a reversed N58-P58 modulation.

3.4. Discussion

The purpose of this study was to examine the cortical mechanisms associated with the stabilization of an object held in precision grip when resisting to periodic/predictable or random/non-predictable external load perturbations. Predictably timed reaction signals provide the opportunity to prepare for a specific response in the case of simple reaction tasks, but also confer an advantage in choice reaction tasks, where temporal preparation optimizes "response readiness". The anticipatory increase in the grip force prior to periodic load application confirms earlier work (Weeks et al., 2000; Boudreau and Smith, 2001) and in particular the findings of a previous study (Kwok and Wing, 2006), where the same manipulandum was used in a similar, although more elaborate task. Our results showed that the rise of the grip force in the predictable condition is accompanied by increased EMG activity, recorded over the first dorsal interosseous muscle (FDI) and, at the cortical level, of higher amplitude slow brain potentials and an overall power reduction in the beta frequency band. Anticipation of the periodic load resulted to a decrease in the LLR's magnitude and in its presumptive motor cortex generator both at

the source and at the scalp level. The preparatory activity probably modulates the long-latency reflex and the sensorimotor activity immediately preceding the reflex, as suggested by the linear correlation between the preparatory slow brain potential and the latter's activity magnitude in terms of dipole strength.

3.4.1. Pre-load period

3.4.1.1.. Anticipatory activity preceding load force perturbations

The preparatory cortical slow-brain potentials have been studied extensively in many studies since they were first reported in the mid-sixties. Walter et al. (1964) published a study about the Contingent Negative Variation, a component which rises in the time interval between a warning and an imperative stimulus. A year later, Kornhuber and Deecke (1965) discussed the presence of the Bereitschaftspotential (i.e. German for "readiness potential") prior to self-generated movements. Preparation for a movement, anticipation of time-predictable stimulus (either in a simple reaction or in a choice task) and even for observation of a predicted movement (Kilner et al., 2004) modulates of the amplitude and the slope of the slow brain potentials. The time course and amplitude of slow brain potentials are influenced by the timing regime of a task not only when participants are made aware of a timing manipulation (Müller-Gethmann et al., 2003) or have an explicit timing instruction (Walter et al., 1964), but also when timing is manipulated in an implicit fashion (Praamstra et al., 2006).

In the present experiment, the sole parameter varied between the two conditions was the regularity of the interpulse interval; the amplitude, duration and location of the perturbation were identical. The slope of the readiness potential was higher in the predictable condition, a finding consistent with previous work (Jahanshahi et al., 1995; Cunnington et al., 1997). Preparatory slow brain potentials were also present in case of unpredictable load force perturbations. However, the slope was much smaller than that in the predictable condition and it probably reflected general anticipation processes. The neural substrates underlying the preparatory slow brain potentials depend on the nature of the task. Preparation for a predictable simple movement was found to depend on primary sensorimotor cortex and medial premotor cortex (Jenkins et al., 2000). Preparation for a temporally predictable choice response also involves lateral (pre)motor structures, as we demonstrated in an earlier EEG study (Praamstra et al., 2006). In the present data, the scalp distribution of the preparatory activity developed a contralateral predominance in the last 200 ms before load onset. This distribution provides support for an association between the preparatory activity and the sensorimotor cortex activity preceding the LLR, i.e. the N58-P58. At the same time, it does not rule out a (possibly earlier) contribution of the medial premotor cortex to the preparatory activity.

The robust preparatory activity evidenced here in slow brain potentials contrasts with remarkably little preparatory activity in single unit responses from cells in primary motor cortex (Picard and Smith, 1992), dorsal and ventral premotor cortex (Boudreau et al., 2001), and the medial wall premotor areas (supplementary and cingulate motor areas) (Cadoret and Smith, 1997). In these studies, preparatory single unit activity was virtually absent notwithstanding the presence of preparatory grip force adjustments, suggesting

that these motor areas are not significantly involved in the elaboration of adaptive internal models of hand-object dynamics (Boudreau et al., 2001). The discrepancy might be due to the slow brain potentials reflecting a general adaptation to the temporally predictable timing regime without actual connection to the mechanisms controlling reflex grip force adjustments. However, while this explanation cannot be entirely ruled out, our finding of a relation between preparatory activity and the amplitude of motor cortical potentials preceding the reflex speak against it. Also relevant to the discrepancy is the fact that the preparatory EEG activity reflects post-synaptic dendritic potentials different from single unit action potentials. The slow brain potentials may modulate cortical excitability and reflex amplitude without direct reflection in cell action potentials. Nevertheless, this still leaves unexplained why there is preparatory grip force adjustment without concomitant spiking activity.

3.4.1.2. Time – Frequency analysis

Several studies have examined the modulation of the alpha and beta frequency bands in motor tasks requiring self-generation of movement or reaction to predictable or random external cues (Leocani et al., 2001; Alegre et al., 2003a, b; Gómez et al., 2004b). The typical pattern is a pre-movement reduction in both bands, usually over the parieto-occipital and motor areas for the alpha and beta band respectively, which is as indication of cortical activation. In agreement to these studies, we recorded solely in the regular condition a significant reduction of the beta band activity predominantly over the contralateral to the movement sensorimotor areas (most likely the primary motor cortex),

which started around 500 ms prior to load onset. Although frequency-specific oscillatory changes and slow brain phasic components presumably reflect different cortical mechanisms (Pfurtscheller and Lopes da Silva, 1999), it is noteworthy that, in both cases, the foci of activation during the last 200 ms before load onset were recorded over approximately the same areas (i.e. contralateral sensorimotor cortex). These findings provide further evidence in favor of the anticipatory nature of the task and the involvement of motor areas in predictive motor control.

3.4.2. Post-load period

3.4.2.1. Motor cortex potentials following load force perturbations

Goodin et al. (1990) described a direct relationship between the amplitude of scalp-recorded vertex maximal EEG potentials and the LLR amplitude. The amplitudes of these cerebral and EMG responses were attenuated after predictable perturbations. MacKinnon et al. (2000) identified a cortical potential, peaking at a latency of 54 ms, whose generator resided in the contralateral to the response motor cortex. The authors considered this source to be the cortical generator of the long latency reflex, elicited by rapid angular wrist displacements. We found a similar component peaking at 58 ms after load perturbation, whose amplitude is modulated by the task (it decreases due to the presence of cortical preparatory activity). In addition, there was a correlation between slow brain potentials (the preparatory activity) and the N58-P58 dipole strength, indicating a possible causal relationship. The timing of the sensorimotor cortex activity represented in

the N58-P58 was consistent with the onset and peak latency of the EMG LLR. This strongly suggests that the long latency reflex is not only transcortical, but also that it is modulated at a central level.

An unfortunate weakness of the present study was that preparatory EMG activity was found for the FDI muscle, but that the LLR modulation of the FDI was not as clear as for the APB. The width of the manipulandum (7.4cm) was very close to many participants' maximal grip aperture, and we suspect that this may have compromised the reflex response in the FDI. A related issue is the possible confounding effect of preparatory EMG amplitude on the LLR. It has been previously shown that the LLR magnitude increases with increased pre-load muscle activity (Marsden et al., 1976); furthermore, Capaday et al. (1994) demonstrated a nearly linear relationship between background EMG activity and LLR magnitude. In our data, across participants and conditions, the LLR magnitude was positively correlated with pre-load EMG activity. The positive correlation between pre-load EMG and LLR magnitude may have attenuated this modulation. Relevant in this context is that the grip force response was modulated in the expected direction with a smaller response after regular than after randomly timed perturbations. While the direction of the modulation can be taken as reliable, the modulation showed a lag relative to the LLR and may have been affected by the cross talk problem causing a grip force response coincident with the load perturbation.

It has to be acknowledged that the N58-P58 was not modulated in isolation. Evoked responses after the N58-P58 (P100, N140) also differed between regular and randomly timed load force perturbations. A reduction in amplitude of median nerve

somatosensory evoked potentials is observed when they are elicited during tactile exploration, movement, or imagined movement (Cheron and Borenstein, 1987; Jones et al., 1989; Huttunen and Hömberg, 1991). A similar movement-related "gating" of evoked responses may have been invoked in the regular condition of our experiment, thus accounting for at least part of the amplitude differences observed. Whether or not the modulation of the N58-P58 involves more than just this mechanism cannot be answered with certainty. While our data suggest a relation of the N58-P58 with the efferent limb of the LLR reflex arc, this needs to be further substantiated by data that show a convincing co-variation of the amplitude of the N58-P58 and the magnitude of the LLR.

The identification of motor cortical potentials preceding reflex grip adjustments might raise the question whether the reflex was cutaneously mediated or due to muscle stretch. Macefield et al. (1996a) suggested that it is only the muscle-stretch mediated reflexes that utilize a trancortical path, not the cutaneous ones. On the other hand, Macefield et al. (1996b) inferred from microneurographic data that the cutaneous afferents are the only suitable receptors for triggering and adjusting the (precision) grip force in response to load perturbations. Further evidence was provided by (Corden et al., 2000) where they stated that the long latency reflex does not originate in muscle stretch receptors, but rather from the skin and/or subcutaneous nerve terminals.

Evidence for the involvement of the primary motor cortex in the generation of reflexive precision grip responses was provided by a recent imaging study (Ehrsson et al., 2007). A question that might be raised by single-cell studies on monkeys (Picard and Smith, 1992; Boudreau and Smith, 2001) is whether the excitation of the motor cortex

neurons results from cutaneous or proprioceptive afferents, since the receptor cells from both types of afferents fire at latencies appropriate for contribution to the long latency reflex. However, Picard and Smith (1992) showed that motor neurons receiving cutaneous afferents are more sensitive in detecting and correcting slip and shear forces generated by applying a load on a holding object, while proprioceptive neural receptors get excited by large loads. Taken together, the possibility of a transcortical route for tactile information triggering the long latency reflex is certainly not contradicted by existing evidence. Comparing this modulation to similar sensory-evoked response data in the MacKinnon et al. (2000) study, which purportedly concerned the muscle-stretch-mediated long latency reflex, it is clear that not only the magnitude of the modulation is stronger, but also that the modulation affects earlier components in our data. These differences might be explained by a greater contribution of cutaneous information in our study versus a stronger contribution of muscle stretch in the MacKinnon et al. (2000) study, but this remains speculative.

3.4.2.2. Time – Frequency analysis

In our study, a beta ERS component, which was evident in both conditions (although significantly stronger in the random one) appeared predominantly over the contralateral primary motor area around 900 ms after load onset. Beta ERS, typically observed over the premotor and/or primary motor areas, occurs after the termination of a motor program (Alegre et al., 2004). It is believed that it is related with the termination of motor command (Leocani et al., 2001), but it may also depend on somatosensory afferents with

an inhibitory effect at the motor cortex (Cassim et al., 2001). Following the first view, the ERS amplitude in the predictable condition was reduced due to overlap with preload ERD induced by the subsequent pulse. An alternative or perhaps complementary view is that the tighter grip in the predictable condition resulted to afferent signal attenuation, consequently reducing the ERS amplitude.

3.5. Conclusion

This study identified movement-related EEG correlates to grip force adjustments preceding predictable load perturbations. Movement-related activity in motor areas of the cortex is expected to accompany anticipatory grip force increase but has not been detected in studies using single-cell recordings in monkeys. The preparatory EEG activity identified in the present study probably also presets relevant structures for the anticipated load force perturbation, thus reducing the long-latency reflex response to predictable compared to randomly timed perturbations. Our data suggest that the locus of this modulation is central reflected in the amplitude modulation of the phasic sensorimotor cortex activity immediately preceding the long latency reflex. In a previous study that also used EEG, McKinnon et al. (2000) did not find a similar central modulation for the muscle stretch-mediated long-latency reflex, although their results supported a transcortical pathway. This difference may reflect a difference between proprioceptive and tactile mediation of the long latency reflex but is perhaps more likely explained by the different ways in which the experiments manipulated preparatory set. Further work is needed, however, to clarify this difference and establish an unambiguous covariation

between sensorimotor cortex activity and reflex amplitude to underpin a central modulation of the long-latency reflex.

Chapter 4

Movement-related changes in cortical excitability: A steady-state SEP approach.

* A modified version of this chapter is currently in press as:

Kourtis D, Seiss E, Praamstra P (In Press) Movement-related changes in cortical excitability: A steady-state SEP approach. Brain Res.

Abstract

This study explored the use of steady-state somatosensory evoked potentials (ssSEPs) as a continuous probe of the excitability of the sensorimotor cortex during the foreperiod and the response time of a cued choice reaction time task. ssSEPs were elicited by electrical median nerve stimulation at the left and right wrist, using a stimulation frequency of 22.2 Hz. Scalp-recorded ssSEPs were analyzed by means of dipole source analysis to achieve optimal separation of left and right hemisphere ssSEPs. The time course of ssSEP modulation at the source level was extracted by means of a wavelet transform. In addition to the extraction of ssSEPs, the analysis included a derivation of lateralized attention and movement-related potentials, i.e. the attention directing anterior negativity (ADAN) and the lateralized readiness potential (LRP). The results revealed a time course of ssSEP modulation remarkably similar to the time course of ADAN and LRP. The time course was characterized by a reduction of ssSEP amplitude at latencies just following the latency of the ADAN (~ 400 ms) and the latency of the LRP (~1200 ms). This reduction was greater for contralateral than for ipsilateral movements. The study demonstrates that ssSEP methodology represents a feasible approach to the measurement of movement-related changes in cortical excitability, which may be used to resolve ambiguities in the interpretation of lateralized event-related brain potentials.

4.1. Introduction

Sensory evoked potentials are small voltage fluctuations generated by the central nervous system following stimulation of the sense organs. Presentation of the stimuli, in a rate sufficiently low for the sensory cortex to recover, gives rise to transient evoked responses, the modulation of which (in terms of latency, amplitude etc.) constitutes common ground of research for "traditional" EEG studies. On the other hand, repetitive stimulation elicits continuous sinusoidal brain responses, oscillating at the same frequency as the driving stimulus, which are called steady-state evoked potentials.

Although steady-state evoked potentials (ssEPs) can be elicited over a range of frequencies from visual, auditory or somatosensory oscillating stimuli, the fundamental frequency of the driving stimulus, which produces the highest amplitude steady-state evoked potentials, is modality specific. It has been well established that in the auditory system, the optimal frequency of the driving stimulus is around 40 Hz (Galambos et al., 1981; Romani et al., 1982; Spydell et al., 1985; Picton et al., 1987; Stapells et al., 1987; Pantev et al., 1996). In the visual system, steady-state evoked potentials are elicited in three frequency ranges in the case of unpatterned flashing stimuli; the ones with the highest amplitude ssVEPs are observed near 10 Hz, followed closely by 18 Hz stimulation; ssVEPs of lower amplitude can be elicited by 50 Hz flashing stimuli. In the case of patterned flashing stimuli the optimal frequency is around 6 Hz (Regan, 1982).

In the somastosensory system, steady-state evoked potentials have been produced by peripherally stimulating the median nerve in frequencies ranging from 12 up to 100 Hz (Namerow et al., 1974). Further research showed that the highest amplitude ssSEPs

are elicited by stimuli oscillating in the 20 Hz frequency range; 26 Hz and 21 Hz were reported by Snyder (1992) and by Tobimatsu et al. (1999) respectively, as the optimal frequency for repetitive somatosensory stimulation.

The transient SEPs which are produced by peripheral stimulation of the median nerve have similar waveforms and topographies whether they are elicited by mechanical vibrations or electrical shocks (Pratt et al., 1980; Pratt and Starr, 1981; Onofrj et al., 1990). The lower amplitudes and prolonged latencies of the mechanically produced SEPs (Wiederholt et al., 1982) are ascribed to "skin indentation and mechanoelectrical transduction at the skin receptors" (Hashimoto et al., 1990) rather than to different cortical processes. Intracranial recordings have showed that the generators of the short-latency (<40ms) (Wood et al., 1988; Allison et al., 1989a) and most of the long-latency transient SEPs (Allison et al., 1989b) are located in the primary somatosensory cortex, contralateral to the stimulating hand. The sources of the steady-state somatosensory evoked fields (ssSEFs: The MEG equivalent of ssSEPs) have also been located in the primary somatosensory cortex. Pollok et al. (2002) reported no significant difference in the location of the ssSEFs and the transient SEFs' sources. However, Nangini et al. (2006), recording simultaneously transient and stead-state SEFs, found the transient SEFs' sources to be located on average 3mm more lateral and inferior to the ssSEPs' sources. Although the validity of this finding can be questioned on the basis of the rather limited spatial resolution of MEG systems (e.g. Volkow et al., 1997), transient and steady-state SEFs demonstrated a different dependency on the interstimulus interval, supporting the notion that they originate from distinct neuronal populations.

Steady-state evoked potentials constitute a continuous measure of the cortical mechanisms governing selective attention and response preparation. In the auditory system, contrary to a previous study (Linden et al., 1987), Ross et al. (2004) demonstrated that the ssAEP's amplitude was enhanced in response to attended compared to non-attended stimuli. Analogous results have been repeatedly found in the visual system (Morgan et al., 1996; Müller et al., 1998; Di Russo and Spinelli, 2002) and by one study regarding the somatosensory system (Giabbiconi et al., 2004). The present study used the ssSEP approach with the aim to explore its feasibility in a motor task and in order to address questions regarding the generation of lateralized movement-related brain potentials.

Numerous studies have shown that the amplitude of short-latency SEPs is reduced before and during active and passive movement ("sensorimotor gating", Cheron and Borenstein, 1987; Cohen and Starr, 1987; Huttunen and Hömberg, 1991; Valeriani et al., 1999; Wasaka et al., 2003; Kida et al., 2004a, 2006b). Pre-movement sensorimotor gating is generated by a centrifugal mechanism, according to which sensory signals are attenuated by the motor command (although a centripetal mechanism also exists during motor execution, according to which the sensory afferents for SEPs interact with sensory afferents induced by movement e.g. Jones et al., 1989), where efferent motor signals modulate the afferent somatosensory signals, which produce the early SEPs (Wasaka et al., 2003; Kida et al., 2006b). It is generally believed that centrifugal gating does not occur at a peripheral level; instead the interaction between the motor and the somatosensory signals take place at cortical or subcortical levels (Starr and Cohen, 1985; Jones et al., 1989; Insola et al., 2004; Wasaka et al., 2005; Kida et al., 2006c).

Preparation for a forthcoming movement is reflected in the lateralized readiness potential (LRP), which develops during the foreperiod between a cue and response stimulus as a result of the differential activity between the contralateral and ipsilateral hemisphere motor cortex (for a review see Eimer and Coles, 2003). The LRP provides an independent measure of the time course of movement preparation allowing a comparison with the information that we aimed to gain from simultaneously recorded ssSEPs. An inherent limitation of the LRP lies in the fact that it is a difference measure between the EEG activity recorded over the hemispheres contra and ipsilateral to the side of movement. Vidal et al. (2003) and Praamstra and Seiss (2005) have suggested that the LRP during movement preparation and execution involves contralateral activation and ipsilateral inhibition. The bi-hemispheric involvement in the preparation of a unimanual response underlines the limitations of the LRP and the potential value of complementing it with ssSEPs. We expected to record decreased ssSEPs amplitudes due to sensorimotor gating, not only during motor execution, but also during the preparatory period, while (asymmetric) motor cortex activity increases, presumably reflected in the development of the LRP.

A further objective of the present study was to clarify the generation of the lateralized ADAN (anterior directing-attention negativity) component, which is derived in the same manner as the LRP and precedes the latter during the fore period between a cue and response stimulus. The ADAN is associated with the executive control of spatial attention (e.g. Hopf and Mangun, 2000; Eimer et al., 2002) and with the selection between response hands or response directions (Verleger et al., 2000a; Praamstra et al., 2005; Gherri et al., 2007). As to the generation of the ADAN, the prevalent view is that it

involves activation of the contralateral frontal cortex, expressed in electrocortical activity of negative polarity, has been challenged by Praamstra et al. (2005) who argued that the ADAN can also be explained by ipsilateral activity of positive polarity serving the suppression of the non-selected response. The modulation of ssSEPs in the time window of the ADAN enables an evaluation of these alternative explanations. We expected to observe a decrease in ssSEPs amplitude during the occurrence of the ADAN, which should be higher either in the hemisphere contralateral to the cued side if the ADAN reflects selection of a motor response or in the hemisphere ipsilateral to the cued-side if the ADAN reflects inhibition of the non-selected response.

One previous study examined the modulation of transient SEPs during the foreperiod of a forewarned reaction time task, but it did not evaluate the effects of response selection (Böcker et al., 1993). Closer to the goals of our study, Eimer et al. (2005) reported enchanced transient SEPs, elicited by tactile stimuli delivered during the foreperiod of a cued choice response task, when stimulation was applied at the cued side. However, the authors applied the stimulation only at two possible delays, therefore limiting their study to two pre-selected points in time, consequently not having a complete picture of the attentional and response selection mechanisms, which operate during the entire foreperiod. In the present study, by contrast, repetitive stimuli were applied during the entire foreperiod (Figure 4.1), producing steady-state somatosensory evoked responses, oscillating at the presentation rate of the driving stimuli. In addition, the stimulation was applied to both hands simultaneously under the assumption that generation of ssSEPs in the contralateral primary somatosensory cortex would enable the

selective recovery of each hemisphere's ssSEP modulation by an analysis at the source level using dipole source modeling.

4.2. Methods

4.2.1. Participants

Six males and 2 females (age: 30 ± 8 yrs), seven of whom were right-handed, took part in the experiment. All had normal or corrected-to-normal vision. None of them had a history of hand injuries, psychological or neurological disorders. All the participants provided their informed consent after full explanation of the study.

4.2.2. Procedure and stimuli

The experiment consisted of a cued choice-reaction task, divided in 8 blocks of approximately 5 minutes each, preceded by a practice block of equal duration. Each block consisted of 80 trials, whose structure is presented in Figure 4.1. Throughout each block four orthogonal brackets delineating a square fixation area were displayed at the center of a computer monitor, along with two square boxes in the left and right lower quadrants.

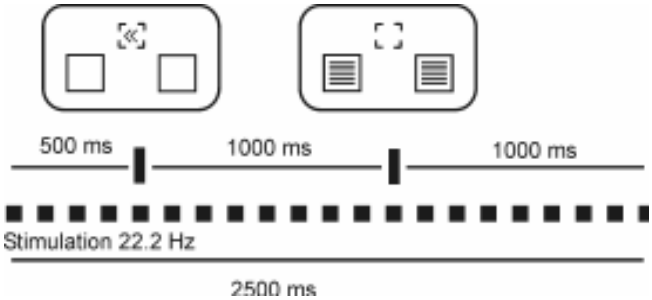

Figure 4.1: Schematic representation of a trial, which includes electrical stimulation (represented by the dotted line). The directional arrows pointed either to the right or the left with equal probability. The "go-signal" was given by the display of horizontal lines (90 % probability) inside the boxes; vertical lines instructed the participants to withhold their response. The visual stimuli in the trials without electrical stimulation were identical.

Each trial started with the display of a directional cue (right or left pointing arrows), presented for 100 ms between the centrally displayed brackets, informing the subjects to prepare a right or left hand response. The arrows were pointing to the right or to the left hemifield with equal probability. Following a cue-target interval of 1000 ms, two identical filler stimuli appeared in the square boxes for 100 ms. In 90% of the trials the stimuli consisted of 5 horizontal lines, which prompted the participants to respond (as swiftly and accurately as possible) using the middle finger of the hand indicated by the preceding arrows. In the remaining 10% of the trials the stimuli consisted of 5 vertical lines, which instructed the participants to withhold the prepared response. The time interval between two successive directional cues was 4000 ms.

Electrical median nerve stimuli for eliciting ssSEPs were applied on alternate trials by a constant current stimulator (Digitimer Ltd model DS7A). Stimulation was

bilateral and applied at the inside of the wrist using bipolar lead attached electrodes (Surface stimulating and recording Silver/Silver Chloride Electrodes, TECA Accessories, Ref No 900X156). The electrical stimulation consisted of trains of square wave pulses (0.5 ms duration each) at a frequency of 22.2 Hz. Each pulse sequence started 500 ms prior to the directional stimulus for a duration of 2500 ms. The magnitude of the electrical pulses was maintained at a value of approximately 60% of the motor threshold throughout the experiment. The motor threshold was determined separately for each participant by unilaterally applying discrete electrical square wave pulses (0.5 ms duration each) at the median nerve at the inside of the wrist. The lowest value which produced a twitch of the thumb (observed by the experimenter) was taken as the motor threshold. This procedure was run separately for each hand.

The experiment was run in a quiet, normally illuminated room. The participants were seated comfortably in an armchair with the forearms placed on the armrests of the chair. The response keys were attached to the armrests, over which the participants placed the middle fingers of each hand. Responses were made by pressing the response key using the middle finger of the left or right hand.

The stimuli were presented in white against a grey background on a 17 inch SVGA monitor at a resolution of 800 x 600. The viewing distance was 100 cm. The brackets, surrounding the directional cue, enclosed a square of 0.75^{o} x 0.75^{o} visual angle, whilst the boxes surrounding the imperative stimuli were squares of 1^{o} x 1^{o} visual angle. The vertical distance between the directional and the imperative stimuli was 1^{o} (centre to

centre) of visual angle, whilst the horizontal distance between the boxes was 2.5^{o} (centre to centre) of visual angle.

4.2.3. EEG data acquisition

EEG was recorded continuously with Ag/AgCl electrodes from 128 scalp electrodes relative to an (off-line) average mastoid reference. The electrodes were placed according to the 10-5 extension of the International 10-20 electrode system (American Electroencephalographic Society, 1994; Oostenveld and Praamstra, 2001) using a carefully positioned nylon cap. Vertical movements were monitored using two bipolar electro-oculography (EOG) electrodes positioned under the left and right eye, while horizontal movements using the nearest to the eyes cap electrodes (FFT9h/FFT10h). EEG and EOG signals were amplified by a BioSemi Active-Two Amplifier and sampled at 1024 Hz.

4.2.4. Data processing

EEG data processing was performed off-line using Brain Vision Analyzer software (Brain Products GmbH). The continuous data were segmented in epochs from 700 ms before to 2300 ms after directional cue onset. Individual trials containing eye movement artefacts were rejected before averaging. No-go trials and trials containing incorrect responses were also removed before averaging. Averages were constructed for each

subject and condition separately. Following averaging, the data were processed to derive lateralized event-related brain potentials (ADAN and LRP). In addition, in order to extract ssSEPs, the data were band-passed filtered between 19 Hz and 25 Hz (Butterworth zero phase-shift filters, 24 dB/octave) (Figure 4.2).

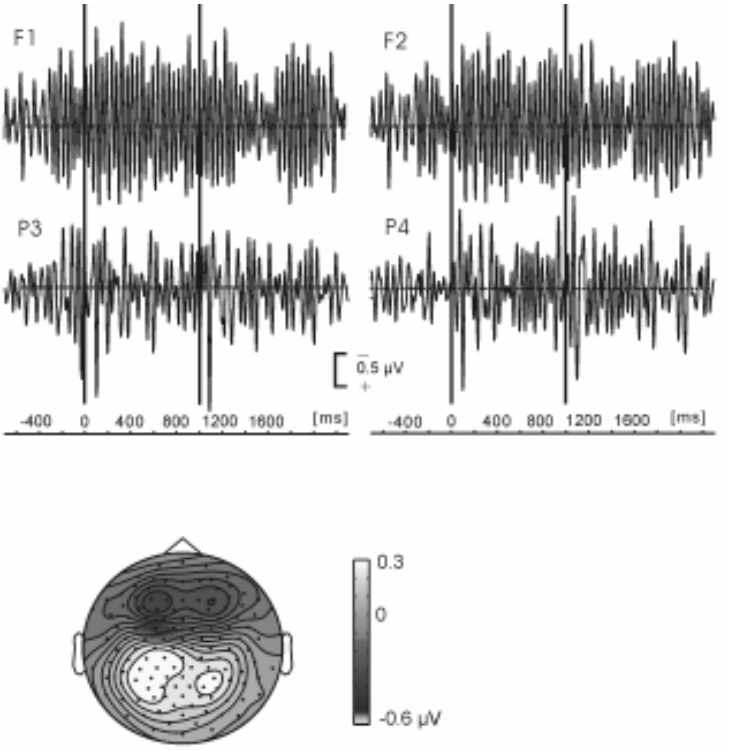

Figure 4.2: Sample ssSEPs as recorded from bilateral frontal and parietal electrodes. The scalp topography (20 ms window over a frontal negative peak) shows distinguishable frontal and parietal maxima in both hemispheres.

4.2.5. Lateralized potentials

The LRP was calculated separately for each condition, by initially computing the voltage difference between homologous electrodes contralateral and ipsilateral to the side of

movement. Subsequently, the difference waveforms were averaged to obtain movement-related lateralized ERP components. LRP amplitude was quantified from pooled electrode pairs (C1/2, C3/4, FC1/2, FC3/4 and FCC3h/4h) in a time window between 800 and 1000 ms after the directional cue. The LRP was preceded by the attention-related ADAN (anterior directing-attention negativity) component, which was quantified from the same selection of electrodes as the mean amplitude between 350 and 450 ms after the cue. The selection of the electrode sites was based on the grand average topographies. The amplitudes of the ADAN and the LRP were compared between conditions by means of t-tests.

4.2.6. Source Localization

The analysis of ssSEPs consisted of the following three steps: (i) dipole source analysis of individual subject ssSEPs, (ii) transformation of scalp ssSEPs of entire trial duration into source waveforms, (iii) extraction of the envelope of the ssSEP source waveforms to analyse the amplitude modulation.

(i) In order to optimize the ssSEP S/N ratio for source analysis, the raw data were divided with respect to the onset of each individual pulse into segments, which contained 4 consecutive median nerve stimulations (length 181.6 ms per segment). The segments were then averaged for each subject separately and band-passed filtered (Butterworth zero phase-shift filters, 48 dB/octave) between 20.2 Hz and 24.2 Hz (i.e. stimulation frequency ± 2 Hz). The resulting data sets (one set per subject) were subsequently

modeled with Brain Electromagnetic Source Analysis (BESA 5.1.6, MEGIS software GmbH). Source analysis was performed on the filtered data using a volume conductor head model, which was a four-shell ellipsoidal head model (head radius 85 mm; brain conductivity 0.33 mho/m; scalp thickness 7 mm and conductivity 0.33 mho/m; bone thickness 7 mm and conductivity 0.0042 mho/m; cerebrospinal fluid thickness 1 mm and conductivity 1 mho/m). Source location was specified in Talairach-Tournoux coordinates, whereas the orientation in theta and phi angles, which correspond to the azimuth and the polar angle, respectively. The feasibility of each source model was assessed by three criteria: a) the residual variance (RV) as a measure of how well a source model explains the recorded data should be minimal, b) the source location and orientation should be in agreement with the scalp topography and c) the source model should be neurophysiologically plausible.

The steep slope (i.e. 48 Hz/octave) produced filtering artefacts at the sides of the segment; for that reason we modeled the two middle cycles (pulses) of the segment. Two symmetrical single dipole sources, located close to the central sulcus, adequately explained the data in all participants (Figure 4.3). This procedure was repeated for each participant separately as well as for the average data and the source models were stored for further processing.

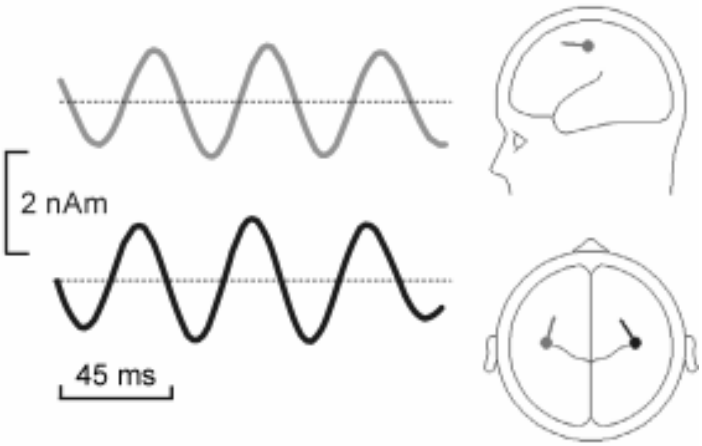

Figure 4.3: Dipole sources and source waveforms, illustrating their symmetrical location in the vicinity of the central sulcus (grand average data).

(ii) In the next analysis step, the averaged segmented data, which contained the entire pulse sequence (i.e. from 700 ms before to 2300 ms after the directional cue) were exported to the BESA software. Following band-pass filtering (Butterworth zero phase-shift filters, 48 dB/octave)) between 20.2 Hz and 24.2 Hz, source analysis was performed, separately for each subject, using the source models that we have previously created (i.e. two symmetrical dipoles). The resulting dipoles waveforms were exported to the Brain Vision Analyzer software for further processing.

(iii) The dipole source waveforms consisted of oscillatory signals (at a frequency of 22.2 Hz), whose amplitude was modulated by the task requirements. To analyse the amplitude modulation, the waveforms were first rectified and then the signal envelopes of the source waveforms were approximated by means of a continuous wavelet transformation (CWT) (complex Morlet wavelet, freq range: 35-54 Hz, freq linear steps:

20, Morlet parameter c=5). Finally, the wavelet frequency band (scale) with centre frequency (i.e. 44 Hz) closest to the oscillation frequency of the rectified signal (i.e. 44.4 Hz) was extracted. The time course of the amplitude modulation of the above-mentioned frequency band sufficiently approximated the envelope of the oscillatory signal (Figure 4.4).

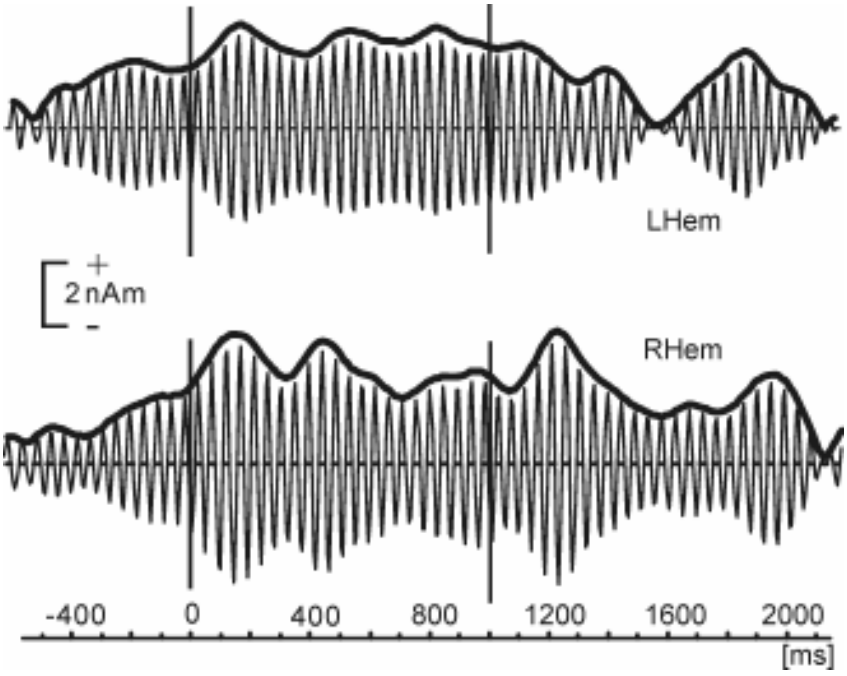

Figure 4.4: Sample ssSEP source waveforms with envelopes. The envelopes were extracted on the basis of the rectified signal using complex Morlet wavelets. The vertical lines at time 0 indicate cue onset and the vertical lines at time 1000 indicate the onset of the imperative signal**.**

Statistical analyses of reaction times, lateralized potentials, and the modulation of ssSEPs were performed using repeated measures ANOVAs in SPSS, as further specified in the text.

4.3. Results

4.3.1. Reaction Times

The reaction times (mean ± SD) were 179.8 ± 49.2 ms and 176.9 ± 48.2 ms for the left and the right hand respectively in the presence of electrical stimulation. For the trials where there was no electrical stimulation, the reaction times were 188.2 ± 53.1 ms and 185.6 ± 49.6 ms for the left and the right hand respectively. A 2 x 2 ANOVA with the factors Electrical stimulation (present vs. absent) and Response hand (left vs. right hand) revealed that the participants responded faster in the presence compared to the absence of electrical stimulation ($F(1,7)=6.3$, $p=0.04$). There was no difference between response hands ($F<1$) nor an interaction between the two factors ($F<1$). The faster reaction times in the stimulation condition may be due to altered sensation in the hand, produced by the stimulation, leading to a lack of modulation in the motor response, i.e. a much stronger force than needed. In addition, the peripheral stimulation itself may have contributed to a brisker movement of the index finger pressing the response button.

4.3.2. Lateralized potentials

The directional information provided by left or right pointing arrows induced transient lateralized activity over the frontocentral scalp area. The earliest lateralization corresponds to the ADAN component peaking around 400 ms after the directional cue (Figure 4.5). The ADAN amplitude in the time window from 350-450 ms after the cue was -0.5 ± 0.4 μV and -0.4 ± 0.4 μV with and without electrical stimulation, respectively.

The amplitude difference was not significant (t<1). The ADAN component was followed by a slowly developing lateralized component, the lateralized readiness potential (LRP) (Figure 4.5). The LRP amplitude during the last 200 ms before the imperative stimulus was -0.6 ± 0.6 μV and -0.4 ± 0.5 μV with and without electrical stimulation, respectively. Again, this amplitude difference was not significant (t(7)=1.13, p=0.30).

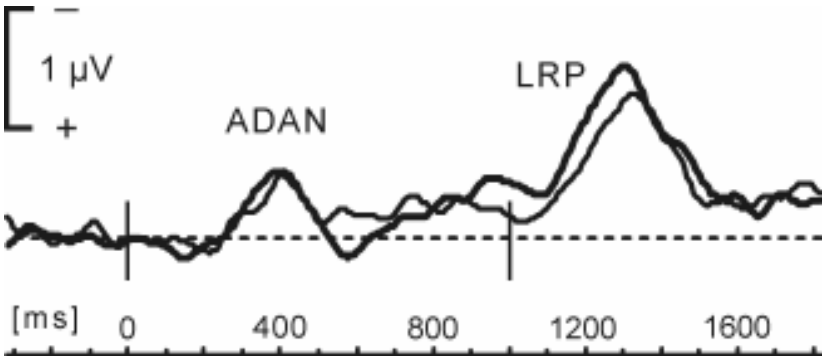

Figure 4.5: Waveforms of the ADAN and LRP derived from grand average data from pooled fronto-central electrode sites (electrode pairs: C1/2, C3/4, FC1/2, FC3/4 and FCC3h/4h). The vertical lines denote cue and imperative stimulus onsets.

4.3.3 Source Waveform Analysis

The next analysis step of ssSEPs was to reduce the 128 channel scalp ssSEP averages to two dipole source waveforms, separately for each condition and subject. The goodness of fit for modeling the two "middle" pulses of the averaged data (see Methods section) was 6.4 ± 3.0%. The Talairach-Tournoux coordinates (Talairach and Tournoux, 1988) correspond to primary sensory cortex generators; for the left (or right) hemisphere source they were x = -(+)36.0 ± 4.3, y = -17.0 ± 6.2 and z = 49.5 ± 2.8. The azimuth and the

polar angle defining source orientation were $\theta = 85.7 \pm 32.1^{o}$, $\varphi = 69.6 \pm 25.4^{o}$ and $\theta = -82.5 \pm 22.2^{o}$, $\varphi = -64.4 \pm 22.7^{o}$ for the left and the right hemisphere source respectively.

The dipole source waveforms represent the time course of ssSEPs recorded over the left and right sensory cortex during the entire trial epoch. To quantify the ssSEP amplitude modulation over time, the signal envelope (Figure 4.4) was extracted using a continuous wavelet transformation (CWT). Figure 4.6 shows the envelopes of the ssSEP source waveforms contra and ipsilateral to left and right hand movement conditions. The time course of the ssSEP modulation was remarkably similar to the time course of ADAN and LRP, in the sense that increased lateralized activity of negative polarity in ADAN and LRP was accompanied by decreased ssSEP amplitudes. The amplitude of the envelopes was analysed in three different time windows defined on the basis of the grand average data, i.e. 375-575 ms, overlapping with the ADAN component, 800-1000 ms, coinciding with the foreperiod LRP, and 1250-1450 ms, immediately following the overt response.

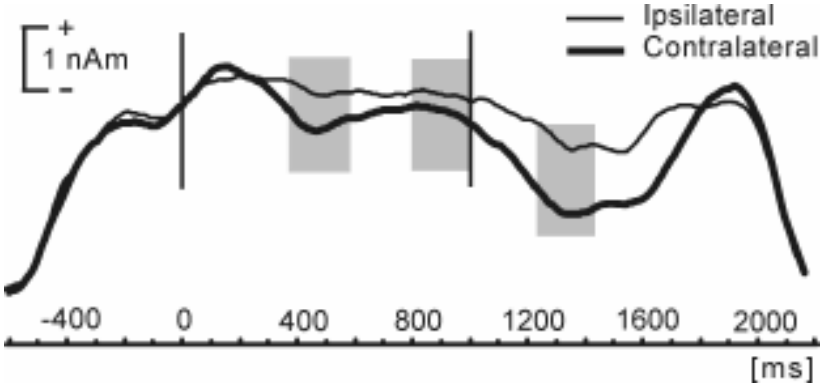

Figure 4.6: Averaged source waveform envelopes of ssSEPs contra and ipsilateral to left and right hand cues. A clear reduction in amplitude around the latency of the ADAN and a more robust reduction following movement execution are evident for ssSEPs in the contralateral hemisphere. The vertical lines denote cue and imperative stimulus onsets. The grey rectangles indicate the time windows for analysis of ssSEPs' amplitude modulation due to interaction with the ADAN (375-525 ms after cue onset), the LRP (last 200 ms before imperative stimulus onset) and movement execution (1250-1450 ms after imperative stimulus onset).

The modulation of the ssSEPs source waveforms during the 375-575 ms interval was assessed by a means of 2 x 2 ANOVA with factors Hemisphere (left/right) and Response side (contralateral/ipsilateral). There was no significant main effect of hemisphere ($F(1,7)=1.8$, $p=0.226$). By contrast, a main effect of Response side ($F(1,7)=6.1$, $p=0.043$) was due to ssSEPs being reduced in amplitude when the contralateral hand was cued, compared to when the ipsilateral hand was cued. As can be seen in Figure 4.7A, this ipsilateral-contralateral difference was very small for the left hemisphere ssSEPs. Post-hoc t-tests confirmed that only the modulation of the right hemisphere source reached significance ($t(7) < 1$ and $t(7)=4.2$, $p=0.004$).

The ssSEP source waveforms were analyzed in the same way in the time window from 800 to 1000 ms, i.e. the last 200 ms of the preparatory period, where no significant modulation was found. By contrast, the ssSEP source waveforms were strongly modulated in amplitude during and after movement (i.e. the button press following the imperative cue). An ANOVA applied to the amplitude values in this time window did not show a significant effect of Hemisphere ($F(1,7)=1.5$, $p=0.254$), but there was again a main effect of Response side ($F(1,7)=14.3$, $p=0.007$). This effect resulted from a greater ssSEP amplitude reduction following contralateral compared to ipsilateral movements. As in the case of the early time window, the asymmetry was more pronounced for the right hemisphere ssSEPs (Figure 4.7B), although it reached significance for both left and right hemisphere ssSEPs ($t(7)=2.7$, $p=0.03$, and $t(7)=3.4$, $p=0.012$, respectively).

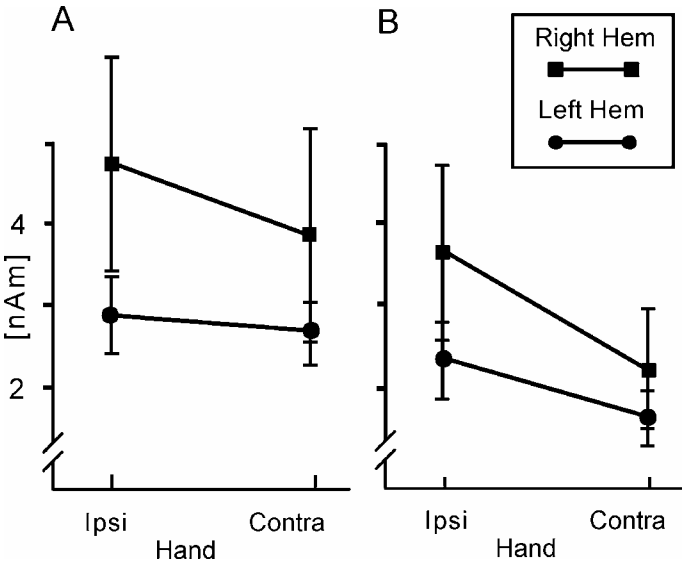

Figure 4.7: (A) Graph representing mean ssSEP source amplitudes for the time interval from 375-575 ms (i.e. time window of the ADAN component). (B) ssSEP source amplitudes for the time interval from 1250-1450 ms. The higher right hemisphere ssSEP amplitude, in both time windows, was caused by a single outlier and was not significant. The vertical error bars represent the standard error of the mean.

4.4. Discussion

The present study used steady-state SEPs to provide a continuous measure of somatosensory cortex excitability during the selection, preparation, and execution of a unimanual response. The use of ssSEPs to probe cortical excitability aimed to provide information complementing the information derived from movement-related potentials. Results revealed an amplitude modulation of ssSEPs whose time course closely resembled the time course of lateralized movement-related potentials. We will first

discuss the results in relation to movement-related potentials and also address some methodological issues.

4.4.1. Source Localization

The morphologies and topologies of SEPs produced either by mechanical or by electrical stimulation are similar, which leads to the presumption that they are mediated by common cortical mechanisms (Pratt et al., 1980; Pratt and Starr, 1981; Onofrj et al., 1990; Hashimoto et al., 1990). The cortical generators of the short-latency SEPs (i.e. latency < 40ms) have a tangential (anterior to posterior and over the central sulcus) orientation and lie in the contralateral primary somatosensory cortex (Nagamine et al., 1992), more specifically in the cytoarchitectonic areas 3b and 1 (Wood et al., 1988; Allison et al., 1989a). Sources of similar location and orientation were also reported for SEPs with latencies of 45-50 ms (Allison et al., 1989b; Hämäläinen et al., 1990).

In the present study, the source generators of the ssSEPs were located in the vicinity of the central sulcus; each source consisted of a single dipole with anterior to posterior orientation. The division of the continuous response (i.e. ssSEP) into four-cycle segments increased the signal-to-noise ratio and the narrow passband filtering separated the ssSEPs generators from other cortical sources. The validity of our method is corroborated by the consistency of our findings with previous studies in which dipole source modelling of the ssSEPs was performed (Snyder, 1992; Münte et al., 1996).

The neurophysiological mechanisms of the ssSEPs' generation remain still unclear. The similarity of our findings to intracranial recordings following discrete median nerve electrical stimulation (Wood et al., 1988; Allison et al., 1989a, b) raises the possibility that the ssSEPs may result from superimposition of transient SEP components. Not far from this assumption, Snyder (1992) argues that the steady-state responses could be equivalent to the P50 component reported by Hämäläinen et al. (1990), which is generated in the primary somatosensory cortex, although precentral contributions should not be entirely ruled out. The belief that transient and steady-state SEPs share the same generators was supported by an MEG study (Pollok et al., 2002); it has been however challenged by another MEG study (Nangini et al., 2006), where the transient and steady-state potentials seem to originate from adjacent but nevertheless spatially distinct generators. The present experiment cannot provide definitive answers to this issue, since transient SEPs cannot be detected when the stimulation frequency exceeds 8 Hz (Pratt et al., 1980).

4.4.2. Signal Envelope Extraction

The extraction of the envelope of an oscillatory signal is typically done by means of the Hilbert transform. However, the lack of time frequency localization feature (Liu and Qiu, 2000) led to alternative methods, such as the Wavelet Transform. The Discrete Wavelet Transform (DWT) offers high analysis speed and has been used for extracting the envelope of various vibrating signals (for example, Tzanetakis and Cook, 2002). The limitation of this method is that it is not possible to study the signal at a specific

frequency. For this purpose, the Continuous Wavelet Transform (CWT) can be used, which in addition offers the ability to select the type of the mother wavelets. Methods, using CWT based on Morlet wavelets, have been proved to effectively extract the envelope of an oscillatory signal (Liu and Qiu, 2000; Sheen and Hung, 2004).

The method used in the present study was based on Continuous Wavelet Transform using complex Morlet wavelet as the mother wavelet. A practical approach was followed based on the capabilities and limitations of the Brain Vision Analyzer software. The oscillatory source waveforms, which were reimported from BESA software, were rectified in order to get the time-course of the signals. The signals have been already strongly filtered around the frequency of interest (i.e. 44.4 Hz for the rectified signal), thus the size of the frequency window around this frequency, as well as the number of frequency steps proved to be insignificant. The sole parameter, which affected the quality of fit between the envelope and the signal, was the Morlet parameter c, which corresponds to the steepness of the frequency distribution of the wavelet function over a certain frequency range (scale). Successive attempts proved that the optimal value for "c" was 4. The results, as shown in the representative Figure 4.4, support the validity of our method.

4.4.3. Task-Dependent Modulation of Source Waveforms

At approximately the latency of the ADAN component (~ 400 ms after cue onset), the amplitude of ssSEPs was modulated as a function of which hand was cued by the cue

signal. ADAN type lateralized potentials following a directional cue were extensively investigated by Eimer (1993, 1995) and, at the time, interpreted as automatic response activation, i.e. as LRP. However, the ADAN derives its name as attention-related component from its association with the executive control of spatial attention (e.g. Hopf and Mangun, 2000; Eimer et al., 2002). More recently, it is recognized that the ADAN not only reflects the control of spatial attention, but is also elicited when a directional cue guides the selection of a manual response, suggesting a role in response selection (Verleger et al., 2000a; Praamstra et al., 2005; Mathews et al., 2006). Source characterization of the ADAN (Praamstra et al., 2005; Mathews et al., 2006) provides evidence for a generation of the ADAN in the dorsal premotor cortex, an area with attention and movement-related functions (Wise et al., 1997; Boussaoud, 2001; Simon et al., 2002). Importantly, as a lateralized component reflecting the voltage difference between homologous electrodes over left and right hemisphere, it is ambiguous whether the ADAN reflects negative polarity activity over the contralateral hemisphere or positive polarity activity over the ipsilateral hemisphere (Praamstra et al., 2005). The current data, with a depression of ssSEP amplitude in the ADAN time window, which was stronger when the contralateral hand was cued, suggest that the ADAN results from an activation of the hemisphere contralateral to the side of a manual response.

The temporal coincidence of the ssSEPs attenuation following a directional cue and the occurrence of the ADAN, which probably originates from the dorsal premotor cortex (Praamstra et al., 2005; Mathews et al., 2006), suggests that the selection between response alternatives affects multiple sensorimotor areas. Attenuation of amplitudes of transient SEPs has been previously observed during movement preparation, prior to

peripheral feedback (Cohen and Starr, 1987; Shimazu et al., 1999; Wasaka et al., 2003), indicating that this effect is central in origin. Voss et al. (2006) used transcranial magnetic stimulation to investigate the characteristics of the efferent motor signal causing sensory attenuation. The authors demonstrated that this efferent signal originates upstream from the primary motor cortex. This result fits well with the ssSEP attenuation in the time window of the ADAN, supporting an interpretation of the ADAN as activity of the premotor cortex associated with the selection and/or covert activation of a motor response (Praamstra et al., 2005; Mathews et al., 2006; Gherri et al., 2007).

The ADAN was followed by a foreperiod LRP representing movement-preparatory activity (see Figure 4.5). One would predict that ssSEPs are reduced in amplitude over the hemisphere contralateral to the prepared response during this time window. Such a reduction was seen for the magnetoencephalographic somatosensory P30m as early as 1500 ms before a self-initiated movement (Wasaka et al., 2003). Although our ssSEP data do show an asymmetry, this effect did not reach significance, possibly due to insufficient power.

During and following the motor response, by contrast, we recorded a robust decrease of ssSEP amplitude, which was greater in the hemisphere contralateral to the response hand. Previous studies on the modulation of somatosensory information during motor preparation have shown effects on transient evoked-potentials dependent on the latency of the component. Whereas during movement execution all components are reduced in amplitude (Böcker et al., 1993), during movement preparation late somatosensory potentials P90 and N140 are enhanced (Böcker et al., 1993; Kida et al.,

2004b; Eimer et al., 2005), while short and middle latency somatosensory potentials N30 and P50 are decreased in amplitude (Böcker et al., 1993; Kida et al., 2004b). The amplitude reduction of the N30 and P50 components is commonly discussed in terms of gating, whereas the enhancement of late components has been associated with attentional mechanisms (Böcker et al., 1993; Eimer et al., 2005). In the present investigation, we used a stimulation frequency of 22.2 Hz, corresponding to an interstimulus interval of 45 ms, which makes it likely that the elicited ssSEPs correspond to short or mid latency transient SEP components. Indeed, such equivalence has also been proposed earlier (Snyder, 1992). From this perspective, the suppression of ssSEPs during movement preparation and execution is in agreement with previous work using transient SEPs.

4.4.4. Methodological Considerations

Our study shows that it is feasible to analyze ssSEPs at the source level and extract meaningful time course information and meaningful asymmetries in the modulation of ssSEPs. With few exceptions (Giabbiconi et al., 2004) steady state evoked response studies have relied on analyses of steady state response amplitude at selected electrodes. Especially with the dipolar field distribution of SEPs, it is a distinct advantage to include all electrodes and achieve a data reduction not through selection of electrodes but by means of a source analysis, as performed here. Such an approach is facilitated by prior knowledge of early and steady-state somatosensory evoked responses being generated primarily in the primary sensory cortex (Allison et al., 1989a; Pollok et al., 2002; Nangini et al., 2006) and by the predominantly contralateral projection of somatosensory

pathways. In spite of this anatomical background, it is possible that asymmetries were diluted by our approach. This is because even with unilateral stimulation, evoked responses can be measured over the ipsilateral hemisphere. The question whether this phenomenon reflects neuronal activation projecting to the ispilareral hand (Cheyne et al., 1995; Chen et al., 1997; Leinsinger et al., 1997) and/or rapid transcallosal intrahemispheric communication (Ilmoniemi et al., 1997; Allison et al., 2000; Nihashi et al., 2005) is yet to be answered. It is therefore important to point out that the here applied approach can be improved by choosing different stimulation frequencies for left and right hand, analogous to previous ssVEP investigations by Müller and co-workers (Müller et al., 1998). Such modification would eliminate 'crosstalk' in the modeling of ssSEPs originating in left and right hemisphere sensory cortex. A further practical point concerns the choice of stimulation modality. While the present study used electrical median nerve stimulation, it is currently more common to elicit ssSEPs with vibrotactile stimulation. Tactile stimulation is also used for eliciting transient SEPs (e.g. Eimer et al., 2005) and is better tolerated as well as less intrusive and has therefore obvious advantages over electrical stimulation in the context of behavioural experiments.

4.5. Summary

Bilateral repetitive electrical stimulation applied on the median nerve of the wrist was used in a cued choice-reaction task. The cortical sources of the elicited steady state somatosensory potentials were localized, by means of dipole sources analysis, in the vicinity of primary somatosensory cortex. The source waveforms were oscillatory signals

modulated by the task parameters; their envelopes were extracted using the continuous wavelet transform. Despite the explorative nature of the present study, in terms of stimulus intensity, pulse duration and interstimulus interval, significant asymmetrical suppression of the ssSEP amplitude was observed during the occurrence of the ADAN and motor execution. The suppression was higher in the hemisphere contralateral to the cued/responding hand; a result compatible with the well-known assumetrical activation of the motor cortex during unimanual responses (see Section 1.7.1.6.). To our knowledge, the present study was the first one to investigate the modulation of the steady state somatosensory evoked potentials at the source level.

Chapter 5

Movement-related EEG evidence for competing representations of multiple pointing directions in premotor and motor cortex

Abstract

Previous neurophysiological work in primates has demonstrated that multiple potential movement direction options are simultaneously represented in the form of activation patterns of neuronal populations of the dorsal premotor and the primary motor cortex. Such activation patterns evolve continuously throughout the preparatory period in a mutually inhibiting manner, until a decision to respond is finally made. The present study investigated whether the operation of this directionally-specific mechanism is reflected in non-invasive population measures of motor and premotor cortical activity in humans. We employed a centre-out pointing task in which response signals were preceded by a precue in the shape of directional arrows pointing to one, two, or three possible adjacent targets. Movement- related potentials were recorded by means of high-density EEG, whereas movement trajectories were monitored by a motion-tracking system. Reaction times showed a scaling from fastest when the precue provided full information on movement direction, to slowest when the precue was least specific. Movement-related potentials associated to motor and premotor cortex preparatory activity demonstrated a corresponding scaling from high to low amplitude. Our results are in agreement with the existence of cortical mechanism, according to which multiple response options are encoded in a continuous and mutually inhibiting way.

5.1 Introduction

Action-related information processing and specification of movement parameters have been traditionally viewed as distinct processes, which are organised in a serial manner (cf. Georgopoulos, 1991; Rosenbaum et al., 1995). However, more recent work has provided strong evidence that motor preparation is organized in a parallel manner, where response parameters are specified in a continuous process. According to this view, a "default" internal representation of the required response undergoes progressive adjustments based on the nature of the task and the information provided by the environment (Hening et al., 1988; Ghez et al., 1989; Favilla et al., 1989, 1990).

These ideas form the basis of the "dynamic field theory of movement preparation" proposed by Erlhagen and Schöner (2002). According to this theory, movement parameters (e.g. direction, amplitude etc.) correspond to dimensions of an activation field, which evolves under the continuous input of information regarding the forthcoming response. Such information is represented in the preshaping of localized peaks of activation, which interact in a cooperative or a competitive mode, reflecting the evolution of the decision process. An imperative signal, defining for example the direction of the required response, will lead to the development of a single activation peak corresponding to the selected movement direction.

In line with this theory, Bastian et al. (2003) investigated neural activity patterns recorded from primates' primary motor cortices during a stimulus-response reaching task, by constructing probabilistic distributions of neuronal populations' activation (DPAs, see Erlhagen et al., 1999) of the whole range of values over the relevant movement parameter

(i.e. direction), The primates were required to perform reaching movements towards one of six circles/targets arranged in a circular configuration. A warning signal indicated one, two or three adjacent circles as possible targets. After the preparatory period, the primate was prompted to reach towards one of the preselected targets as fast as possible. In agreement to earlier studies, movement direction was represented in motor cortical neurons even prior to movement execution (Georgopoulos et al., 1989). Furthermore, the DPAs displayed a single sharp peak in the case of full prior information. When two or three possible targets were predefined, the peak was broader, presumably reflecting the range of possible response directions and was also smaller in amplitude, indicating the possible inhibitory interaction between neural populations representing different directional options.

Analogous findings have been reported in the domain of visuomotor attention (Tipper et al., 1998). Action selection is based on an inhibitory mechanism, where representations of a (small) number of potential targets are processed in parallel in a mutually suppressive fashion. Further evidence for the existence of such an inhibitory mechanism regarding visual attention has been provided by single-unit recordings from primates (Moran and Desimone, 1985; Chelazzi et al., 1993; Connor et al., 1997). However, the correspondence of single-unit recordings from primates to non-invasive recordings in humans is not a straightforward issue. Although, no causal relationship has been established among them, several studies, based on the similarity between ERPs and primates'neuronal activity, have attempted to bridge this gap (Paller et al., 1992; Luck et al., 1997; Shah et al., 2004; Philiastides and Sajda, 2007). The most compelling results come from the domain of visual attention. Luck et al., (1997) in a human EEG study

reported similar attentional modulations of the N2pc component (see Section 1.8.4.1) to neuronal response in primates' visual cortex. Furthermore, Woodman et al. (2007) employed a visual attention task to demonstrate the existence of a monkey homologue of the N2pc. Closer to the topic of our study, Kastner et al. (1998), in a visual attention task, reported patterns of BOLD activity in the human visual cortex, compatible with the concept of mutual suppressive interaction between neural representations of multiple stimuli. The correlation between ERPs and the BOLD response is not clear either; however, a tight covariation between the two measures has been often been observed in a variety of tasks (e.g. Otzenberger et al., 2005; Schicke et al., 2006; Khader et al., 2007).

Cisek and Kalaska (2005) have previously shown in a choice reaction task using monkeys, that decision making and planning is represented in the dorsal premotor cortex (PMd) in the form of directional tuning of local neural populations. They found that PMd cells encode a range of values for a given movement parameter (e.g. direction) and that the level of cell's activity corresponds to the level of (un)certainty of the impending action. Importantly, peaks of neural activation, representing distinct movement options, compete continuously against each other; such competition can be biased by input from the sensory system and/or other brain structures (e.g. basal ganglia), which causes the rise of a single peak over a "decision threshold value" and the concurrent suppression of the peaks corresponding to task-irrelevant options.

Taking into account the afore mentioned studies and the Bayesian view of probabilistic representation of information in the brain (Sanger, 2003; Knill and Pouget, 2004), Cisek (2006) proposed a computational model for integrating action selection and

specification, which forms the basis of the "affordance competition hypothesis" suggested by Cisek (2007). The term "affordances" created by Gibson (1979) refers to the action possibilities as perceived by the potential actor. The "affordance competition theory" suggests that behaviour is determined by the continuous competitions between internal representations of the available action possibilities. An important aspect of this theory is that the encoding of movement parameters (action planning) and the selection of the appropriate response (decision making) occur in the same neural substrate. These processes take place along the dorsal visual stream primarily in the reciprocally interconnected posterior parietal (PPC) and dorsal premotor cortices (PMd) and to a lesser degree in the primary motor cortex (M1), while areas such as the prefrontal cortex and the basal ganglia provide biasing inputs. Neuronal populations in these areas encode all potential parameters of movement in a continuous and mutually inhibiting manner. As a result, when an organism is faced with multiple movement options the summed neuronal activity which corresponds to each option is lower. Consequently, when a decision is finally made in the PMd, the time required to reach to a level of activation, which will trigger the planned response through M1, is longer. At the peripheral level, this prediction agrees with the well-established effect of the increase of reaction times with the number of available movement options (Bertelson and Boons, 1960).

The objective of the current study was to study the encoding of multiple potential actions in humans using non-invasive EEG. We employed a bimanual paradigm where participants, following visual stimuli, which provided information about movement direction, performed short sliding movements towards one, two or three targets located in the right hemispace using the right hand and towards targets located in the left hemispace

using the left hand. We predicted that the activation of (pre)motor areas during response preparation would be inversely related to the number of potential targets. The participants' movements were tracked by means of a motion capture system. The experimental design allowed the subtraction of non-lateralized activity in order to isolate lateralized motor activity. Furthermore, we used centrally presented cues, which are known to elicit dorsal premotor activation related movement direction (Praamstra et al., 2005). In addition, high-density EEG allows, apart from obtaining data with excellent time resolution, the identification of cortical activity originated from motor structures.

The amplitude of the Contingent Negative Variation (CNV, Walter et al., 1964), which during its late phase is associated to activation of primary motor and premotor areas was expected to decrease in amplitude with the number of potential targets. A similar effect was expected for the amplitudes of lateralized event potentials developing during the foreperiod, which originate from the PMd (Anterior Directing Attention Negativity (ADAN), Praamstra et al., 2005) and the MI (Lateralized Readiness Potential (LRP), Praamstra et al., 1999). In motor tasks, these components reflect the activation of the contralateral hemisphere to a cued response side, due to allocation of spatial attention (ADAN), response selection (ADAN, LRP) and response preparation and execution (LRP) mechanisms. The possibility of the ADAN reflecting inhibition of the rejected behavioural options (Praamstra et al., 2003) is not very strong, as we demonstrated in Chapter 4. The LRP as well as the late phase of the CNV are strongly related to motor preparation facilitatory processes (cf. Leuthold et al., 2004) and they are typically associated to faster reaction times (e.g. Coles, 1989; Mathews et al, 2006). As a result, we also anticipated reaction times to be longer as the number of potential targets increased.

5.2. Methods

5.2.1. Participants

Nine males and seven females (age: 30 ± 6 yrs), fourteen of whom were right-handed, took part in the experiment. All had normal or corrected-to-normal vision. None of them had a history of hand injuries, psychological or neurological disorders. All the participants provided their informed consent after full explanation of the study. The study was approved by the South Birmingham Research Ethics Committee.

5.2.2. Procedure and stimuli

The experimental paradigm was a precued choice-response task with stimuli presented on a computer screen. The precue stimulus, consisting of one, two or three directional arrows, designated an equal number of potential targets located on a cardboard in front of the participants. Following a foreperiod of 1200 ms, an imperative stimulus, consisting of a single arrow, always fully specified the target towards which the participants had to perform a short and swift reaching movement.

Throughout each block, six circles were displayed on a PC monitor. Three of them were displayed on the left and three on the right hemispace, arranged in such a configuration as to form a conceivable circle, whose centre, indicated by a focusing dot, was located right at the centre of the monitor. The precue stimulus consisted of one, two or three arrows pointing either left or right with equal probability, towards a

corresponding number of circles. The imperative stimulus consisted of one arrow pointing towards one of the circles, which were previously indicated by the precue stimulus as potential targets; in addition, the target circle along with the circle displayed symmetrically over the opposite hemispace were highlighted in order to facilitate the participant's response and provide symmetrical visual input.

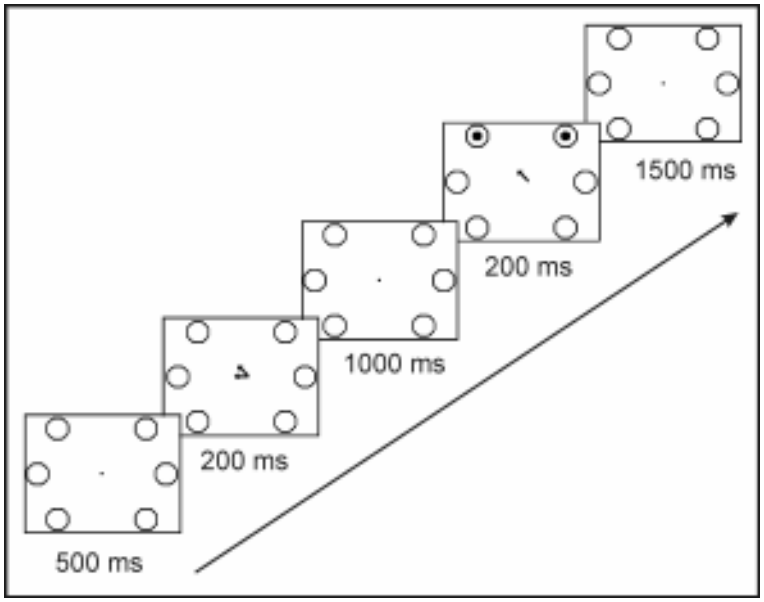

Figure 5.1: Representative example of a trial (2-arrow condition). The precue stimulus is presented 500 ms after the start of the trial. It consists of two arrows pointing towards two circles at the left hemispace. The imperative stimulus is presented 1000ms after precue stimulus offset. It consists of one arrow pointing towards one of the circles that was previously highlighted by the precue stimulus as potential target. At the same time, the selected circle and the corresponding one at the right hemispace are highlighted in order to facilitate the participant's response and also to provide symmetrical visual input.

The experiment was divided in 12 blocks of approximately 4 minutes each, preceded by a practice block of equal duration. Each block consisted of 72 trials. The precue stimulus was presented 500 ms after trial onset. The interstimulus and intertrial intervals were kept constant, 1200 ms and 3400 ms respectively. Each stimulus was presented for 200 ms (Figure 5.1).

The experiment was run in a quiet, normally illuminated room. Stimuli, providing movement instructions, were presented in white over a grey background on a SVGA monitor. The distance between the participants' eyes and the SVGA monitor was 100 cm. Three circular targets (radius = 0.3^{o} visual angle) were displayed on the left hemispace and three on the right hemispace, arranged in such a way as to form a conceivable circle (radius = 1.7^{o} visual angle). The angular distance between targets, at each hemispace, was 45^{o}. The length of each directional arrow was 0.6^{o} visual angle

The participants were seated comfortably in an armchair with the forearms placed on the armrests of the chair, facing a computer monitor. A rectangular piece of thick white cardboard was placed on the armrests of the chair, right in front of the participant. Six square targets (3cm x 3cm made of brown duct tape, named end points) were placed on the cardboard in such arrangement as to form a conceivable circle of 11.5 cm radius, whose centre was aligned with the midline of the participant's body and located 17 cm from the edge of the cardboard. Three square targets were placed on the left side and three on the right side of the circle, corresponding to the configuration of the visual stimuli. The angular distance between those targets, at each hemispace, was 45^{o}. Two

additional, equally sized targets (starting points) were placed centrally, left and right of the centre of the conceivable circle; their distance was ~1mm.

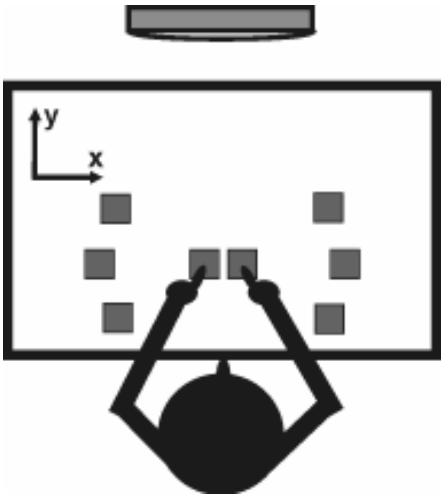

Figure 5.2: Experimental setup

Throughout each block, the participants placed their index fingers on the centrally located targets (starting points) on the surface of the cardboard (Figure 5.2). The precue stimulus always designated the responding hand and provided full or partial information about the direction of the reaching movement, depending on the number of the circles indicated as potential targets. The movement direction was conclusively specified by the imperative stimulus, which prompted the participant to perform a sliding movement towards the corresponding target on the cardboard.

5.2.3. Data Acquisition

Two retroreflective markers were attached on the index fingers' nails of the participants. The movement of the markers was tracked by three motion capture cameras (ProReflex MCU 240, Qualisys AB, Sweden). The cameras were capturing data from 500 ms before to 1500 ms after the display of each imperative stimulus, sampling at 200Hz.

EEG was recorded continuously with Ag/AgCl electrodes from 128 scalp electrodes relative to an (off-line) average mastoid reference. The electrodes were placed according to the 10-5 extension of the International 10-20 electrode system (American Electroencephalographic Society, 1994; Oostenveld and Praamstra, 2001**)** using a carefully positioned nylon cap. Vertical and horizontal eye movements were monitored using two pairs of electro-oculography (EOG) electrodes positioned below the left and the right eye and lateral to the left and the right eye. EEG and EOG signals were amplified with a band-pass of 0-128 Hz by BioSemi Active-Two Amplifiers and sampled at 512 Hz.

5.2.4. Data processing

5.2.4.1. Motion tracking – Reaction Times

Reaction times were calculated according to the following procedure. The position of each marker at the onset of the cameras (i.e. 500 ms before the imperative stimulus) was defined as the starting point. Each marker was initially assigned with coordinate values of

(0, 0). The movement of each marker (consequently of each hand) was examined separately. The velocity threshold which signified movement onset, was set to 80mm/sec. Trials where participants were moving at the onset of the recording interval were rejected. Additionally, trials where movement onset occurred earlier than 100ms before or later than 800 ms after the display of the imperative stimulus were rejected. Trials where bimanual movement was recorded or where a hand moved towards the incorrect hemispace were also rejected. The criterion for erroneous movement was 2cm deviation from the starting point. The percentage of rejected trials over the whole number of trials (mean ± SEM) was 14.0 ± 4.8%, 3.7 ± 0.8%, 2.9 ± 0.7%, for the 1-, 2- and 3-arrow conditions, respectively.

5.2.4.2. EEG Data

The first stage of EEG data processing was preformed using Brain Electrical Source Analysis software (BESA V. 5.1.8, MEGIS software GmbH, Gräfelfing, Germany). The continuous EEG data were segmented off-line in epochs from 500ms before to 2000ms after the informative stimulus. Individual trials containing eye-movements and other artefacts were removed before averaging. All EEG signals were analyzed with respect to an average mastoids reference. The baseline was defined as the time period from 200ms before until the onset of the precue stimulus. Following this procedure, the segmented and artefact-free data were exported to BrainVision Analyzer software (BrainProducts GmbH, Gilching, Germany) for further processing and statistical analysis. Averaged data were created for each participant and condition separately.

One component of interest was the Contingent Negative Variation (CNV) (Walter et al., 1964), which is a slow brain potential in the form a sustained negativity developing during the foreperiod interval. The CNV amplitude was quantified during the last 200ms before the imperative cue from pooled electrode pairs, selected on the basis of scalp topographies (see Results).

Of particular importance was the study of lateralized movement and attention related activity, developing during the foreperiod, which was evaluated by deriving lateralized event related potentials. The derivation was calculated as follows: activity recorded at electrodes contralateral to the side of the cued response was subtracted from activity recorded from homologues electrodes at the ipsilateral side. Subsequently, the difference waveforms associated with left and right side were averaged yielding lateralized ERPs. The amplitude of the lateralized-ERPs was quantified as the mean activity from pooled electrodes over selected time intervals, selected on the basis of scalp waveforms and their respective topographies (see Results).

Statistical analyses of reaction times, lateralization potentials and the modulation of the CNV were performed using repeated measures ANOVA and one tailed post hoc t-tests in SPSS, as further specified in the text.

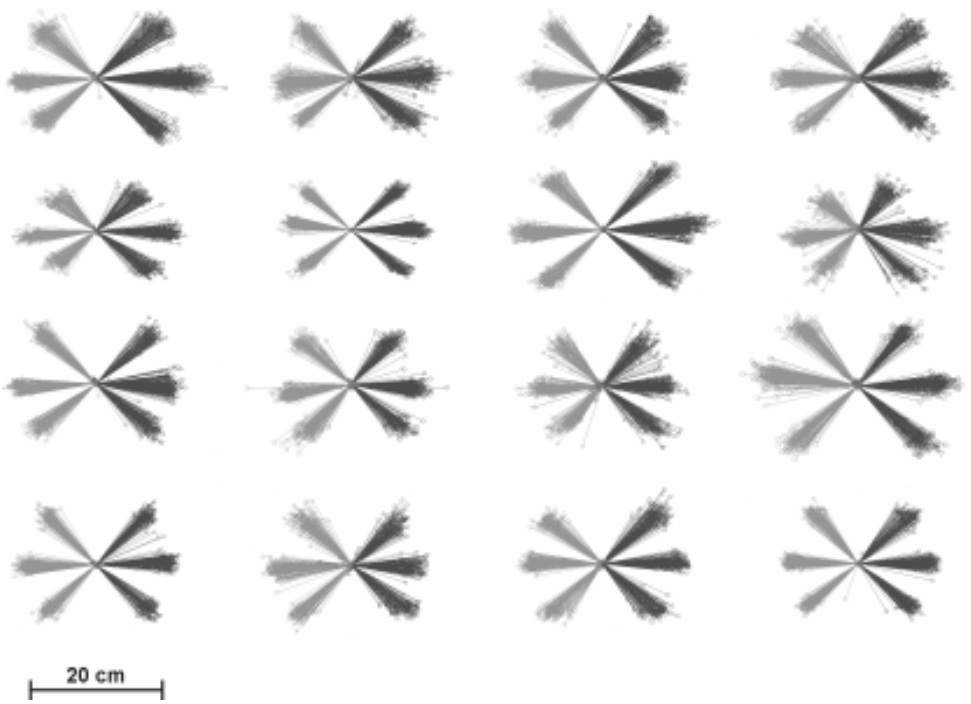

Figure 5.3: Marker trajectories from all participants. The markers were placed on the index fingers' nails. The position of each marker 500ms prior to the imperative stimulus was automatically considered as the staring point (coordinates: (0,0)).

5.3. Results

Although the hands were not screened-off from view, participants performed the task without visual control, as they had to maintain their gaze and attention focused on the monitor in front of them. The movement trajectories (Figure 5.3) show that the task was performed with remarkable accuracy. Given this level of performance and in view of the fact that EEG analyses focused on preparatory activity, no further selection of trials based on performance was performed for subsequent reaction time and EEG analyses.

5.3.1. Reaction Times

The reaction times were 287 ± 87 ms, 353 ± 84 ms and 371 ± 79 ms for left hand responses to leftward pointing one, two and three arrows, respectively and 288 ± 85 ms, 354 ± 78 ms and 377 ± 73 ms for right hand responses to rightward pointing one, two and three arrows, respectively. A 3x2 ANOVA (factors: number of arrows and responding hand) showed a significant effect of the number of arrows ($F(1,15) = 87.372$, $p < 0.001$). No significant effect was found between left and right hand responses ($F(1,15) = 0.618$, $p = 0.444$), nor a significant interaction ($F(1,15) = 1.849$, $p = 0.180$). After pooling left and right hand responses, t-tests (Bonferroni adjusted alpha level: 0.025) showed that there was a significant scaling between conditions: $t(15) = -8.738$, $p < 0.001$ for the 1-arrow vs. 2-arrow condition and $t(15) = -8.010$, $p < 0.001$ for the 2-arrow vs. 3-arrow condition.

5.3.2. EEG analyses

5.3.2.1. CNV

A CNV - like slow negative wave which developed in the time interval between the precue and the imperative stimulus was evident in all three conditions. The CNV amplitude was quantified as the mean amplitude during the last 200ms before the imperative stimulus from pooled electrode sites (Cz, C2, FCC2h and CCP2h for left hand movements and Cz, C1, FCC1h and CCP1h for right hand movements), selected on the basis of scalp topographies (see Figure 5.4).

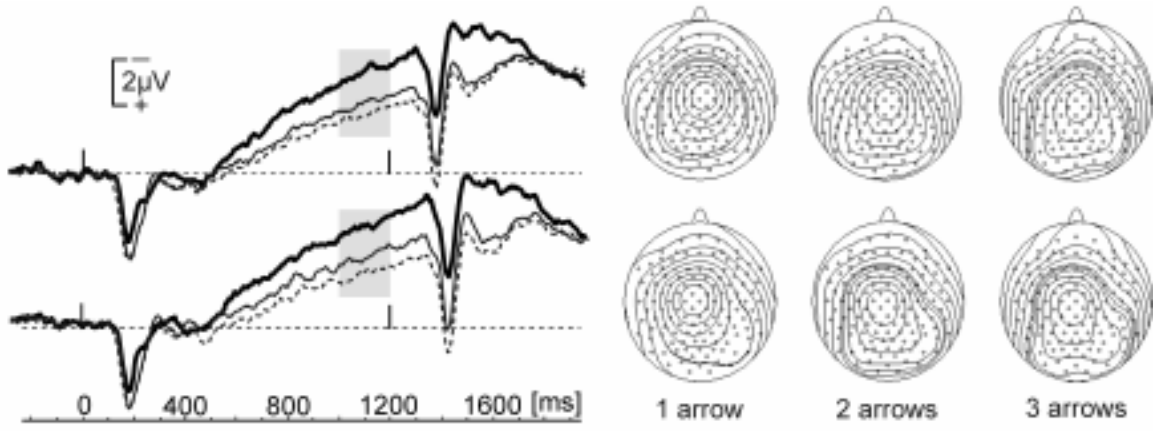

Figure 5.4: *Top part*: CNV waveforms derived from pooled electrodes sites (Cz, C2, FCC2h and CCP2h) during left hand movements and their respective scalp topographies. *Bottom part:* CNV waveforms derived from pooled electrodes sites (Cz, C1, FCC1h and CCP1h) during right hand movements and their respective scalp topographies. The 1-, 2- and 3- arrow condition is represented by the thick solid line, the thin solid line and the thin dashed line, respectively. The small vertical lines at time 0 and time 1200 ms correspond to the onset of the precue and the imperative stimulus, respectively. The horizontal dotted lines denote baseline.

Importantly, the amplitude of this component depended on the amount of information provided by the precue stimulus, being higher in the 1-arrow condition, where the target direction was fully specified and lower in the 3-arrow condition where the precue stimulus provided the least specific information. Specifically, the CNV amplitude for left hand movements was -8.2 ± 2.8 μV, -6.1 ± 3.3 μV and -5.8 ± 3.0 μV for the 1-, 2- and 3-arrow conditions respectively, whereas for right hand movements it was -7.4 ± 2.8 μV, -6.3 ± 3.3 μV and -5.0 ± 2.8 μV for the 1-, 2- and 3-arrow conditions

respectively. A 3x2 ANOVA (factors: number of arrows and responding hand) showed that the CNV amplitude in the selected ROIs significantly depended upon the number of arrows ($F(1,15) = 21.400$, $p < 0.001$). There was no significant effect of responding hand ($F(1,15) = 1.121$, $p = 0.307$), nor a significant interaction ($F(1,15) = 1.790$, $p = 0.186$). After pooling left and right hand responses, post-hoc t-tests (Bonferroni adjusted alpha level: 0.025) demonstrated that there was a significant difference between the 1- and the 2- arrow condition ($t(15) = -3.892$, $p = 0.001$), as well as between the 2- and the 3-arrow condition ($t(15) = -2.521$, $p = 0.023$.

5.3.2.2. Lateralized potentials: ADAN and LRP

The earliest lateralized activity was recorded over occipital electrodes in the time interval 170 to 190 ms after precue onset (Figure 5.5). Its topography and amplitude scaling between conditions suggest that it was generated by the precue asymmetry due to the presence of the arrowheads, being higher in the 3-arrow condition and practically absent in the 1-arrow condition.

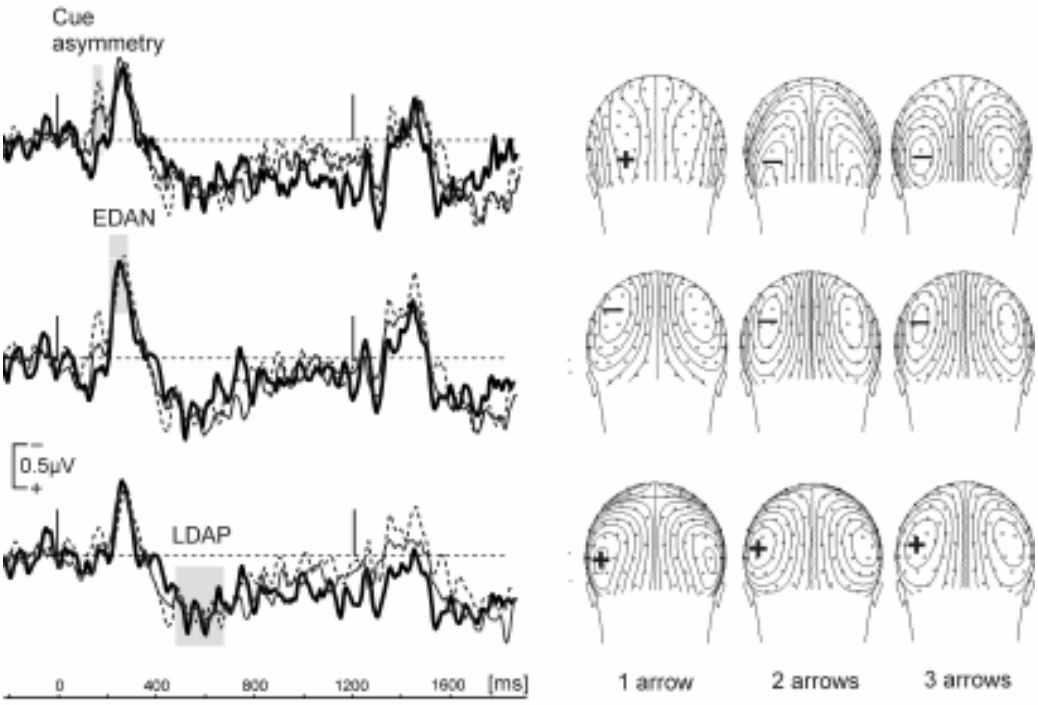

Figure 5.5: Parietal and occipital lateralized activity and their respected topographies derived from pooled electrode pairs (Cue asymmetry: PO7/8, POO9h/10h and PPO9h/10h – EDAN: P3/4, P5/6, CPP5h/5h and PPO5h/6h – LDAP: P7/8, TP7/8, TPP7h/8h and TPP9h/10h). The small vertical lines at time 0 and time 1200 ms correspond to the onset of the precue and the imperative stimulus, respectively. The horizontal dotted lines denote baseline.

The first occurrence of lateralized activity evoked by the directional information conveyed by left and right pointing arrow(s) was recorded over fronto-central and parietal scalp areas. The frontocentral lateralization, which corresponds to the ADAN component (Figure 5.6), consisted of a broad negative wave between ~200-500 ms after the cue, which peaked at ~400 ms. Remarkably, the parietal lateralization demonstrated an early peak at ~275 ms with a parietal maximum, which probably corresponds to an unusually robust EDAN component (early directing-attention negativity; see below). The ADAN

amplitude was quantified from pooled electrode pairs (FC1/2, FC3/4, FCC3h/4h and FFC3h/4h) in a time window between 375 and 425 ms after the directional cue. Similarly to the CNV, the amplitude of the ADAN was higher in the 1-arrow condition and lower in the 3-arrow conditions. A 3x1 ANOVA (factor: number of arrows) showed that the scaling of the ADAN amplitude between conditions was statistically significant ($F(1,15) = 12.066$, $p < 0.001$). Post-hoc t-tests (Bonferroni adjusted alpha level: 0.025) demonstrated that there was a significant difference between the 1- and the 2- arrow condition ($t(15) = 2.269$, $p = 0.019$), as well as between the 2- and the 3-arrow condition ($t(15) = 2.585$, $p = 0.011$).

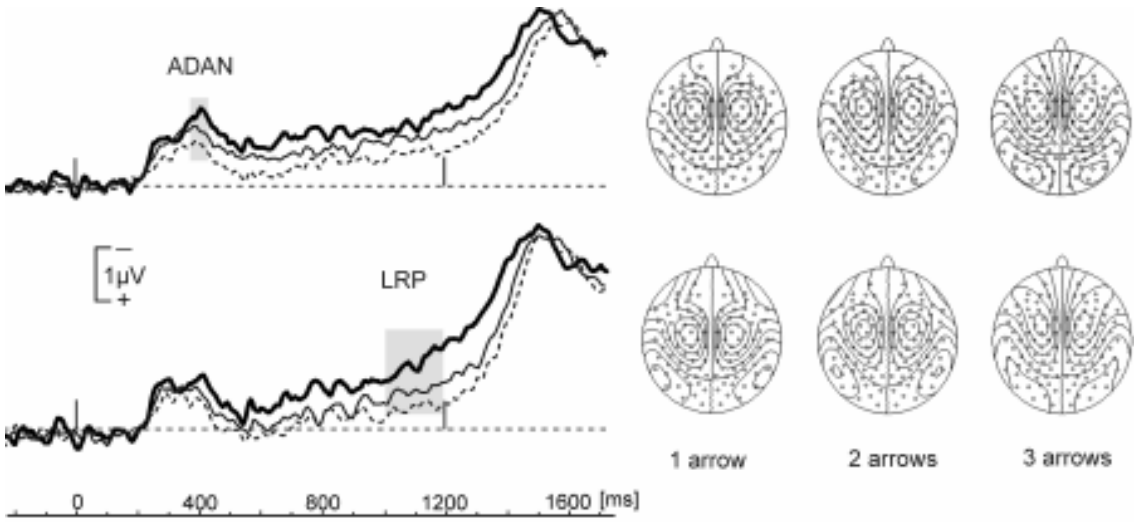

Figure 5.6: Waveforms of the ADAN and the LRP components and their respective topographies derived from pooled electrode pairs: FC1/2, FC3/4, FCC3h/4h and FFC3h/4h for the ADAN derivation and C1/2, C3/4, FCC3h/4h and CCP3h/4h for the LRP derivation. The 1-, 2- and 3-arrow conditions are represented by the thick solid line, the thin solid line and the thin dashed line, respectively. The small vertical lines at time 0 and time 1200 ms correspond to the onset of the precue and the imperative stimulus, respectively. The horizontal dotted lines denote baseline.

The ADAN was followed by the LRP component, which reflects movement related lateralized activation (Figure 5.6). The LRP, although not evident from Figure 5.6 in the cases of partial information, was generated in more posterior sites relative to the ADAN. This becomes clearer when we compare the scalp topographies of the difference between 2- and 3-arrow condition in time windows corresponding to the ADAN and the pre-response LRP (Figure 5.7). Hence, the LRP amplitude was quantified from pooled electrode pairs (C1/2, C3/4, FCC3h/4h and CCP3h/4h) in a time window between 200 and 0 ms before the imperative cue. The LRP amplitude was also higher in the 1-arrow condition and lower in the 3-arrow condition. A 3x1 ANOVA (factor: number of arrows) showed that the scaling of the ADAN amplitude between conditions was statistically significant ($F(1,15) = 23.512$, $p < 0.001$). Post-hoc t-tests (Bonferroni adjusted alpha level: 0.025) demonstrated that there was a significant difference between the 1- and the 2- arrow condition ($t(15) = 4.001$, $p = 0.001$), as well as between the 2- and the 3-arrow condition ($t(15) = 4.385$, $p = 0.001$).

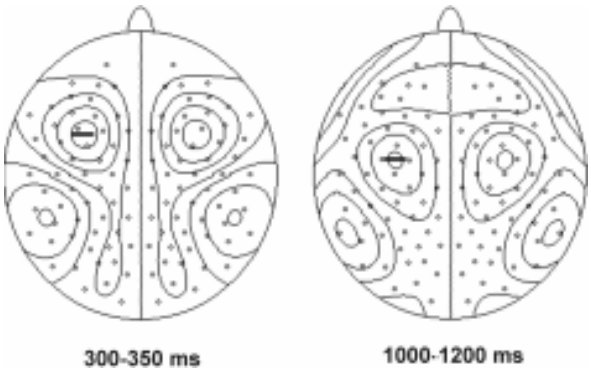

Figure 5.7: Scalp topographies of the difference in lateralized activity between the 2- and the 3-arrow condition.

Shortly after the ADAN onset, the LDAP (late directing-attention positiviy) component was elicited over parietooccipital sites, peaking at about 600 ms after the directional cue (Figure 5.5). The LDAP, most likely generated in the lateral occipitotemporal cortex (Praamstra et al., 2005; Mathews et al., 2006), is related to supramodal attentional control (e.g. Eimer and van Velzen, 2002; Seiss et al., 2007) and possibly reflects the updating of the actor's body representation (Praamstra et al., 2005). In the present study, LDAP amplitude was quantified from pooled electrode pairs (P7/8, TP7/8, TPP7h/8h and TPP9h/10h) in a time window between 500 and 700 ms after the directional cue. The LDAP amplitude was almost identical in all three conditions (3x1 ANOVA, factor: number of arrows, $F(1,15) = 0.002$, $p = 0.997$), hence this component will not be discussed any further.

One might argue that the amplitudes of the above-mentioned lateralized potentials were significantly affected by eye-movements towards the peripheral targets. However, it is clear from Figure 5.8 that the lateralized activity recorded by the vertical and horizontal electrooculography electrodes was small (rarely more than 1μV) during the entire foreperiod and most importantly there was no difference between conditions.

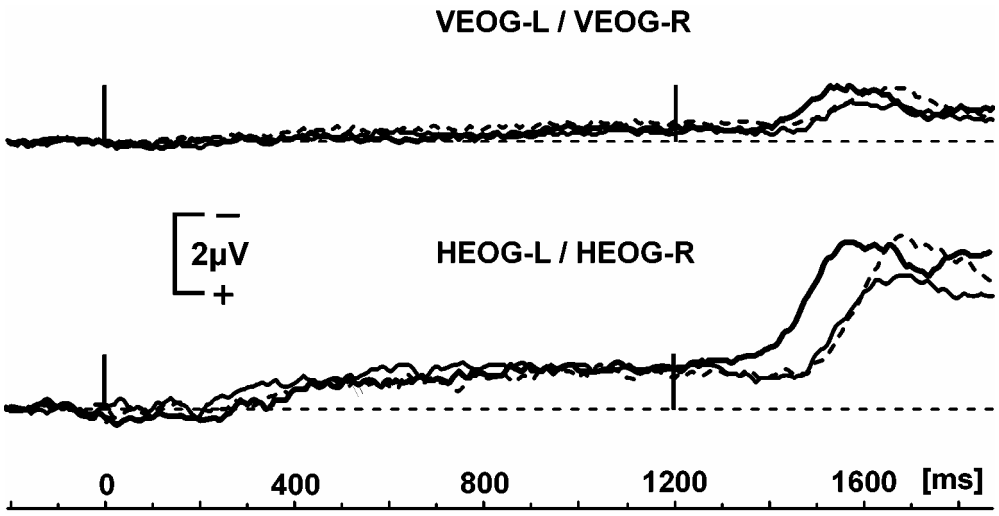

Figure 5.8: Waveforms of lateralized activity recorded by vertical (VEOG-Left and VEOG_Right) and horizontal (HEOG-Left and HEOG_Right) electrooculography electrodes. Lateralized activity due to eye movements was minimal and most importantly there was no difference between conditions. The 1-, 2- and 3- arrow conditions are represented by the thick solid line, the thin solid line and the thin dashed line, respectively. The small vertical lines at time 0 and time 1200 ms correspond to the onset of the precue and the imperative stimulus, respectively. The horizontal dotted lines denote baseline.

5.3.2.3. EDAN and parietal ERPs

As mentioned in the previous section, a rather surprising finding was an unusually prominent EDAN component, which was possibly related to the nature of the task, consisting of a directional movement not often used in movement-related EEG research. It is clear (Figure 5.5) that, although there was no scaling of the EDAN as a function of the information conveyed by the directional cue, the posterior N2 from which the EDAN is derived, displayed a contralateral-ipsilateral amplitude asymmetry and a clear

modulation by cue information (Figure 5.9). To quantify this modulation, a subtraction of the 1- and 3-arrow condition was performed to outline the N2 scalp topography, yielding bilateral posterior parietal maxima, captured by two electrode pools consisting of P3, P5, CPP5h, and PPO5h (left scalp) and P4, P6, CPP6h, and PPO6h (right scalp). A 3 x 2 x 2 ANOVA (Number of arrows by Hand by Hemisphere (contralateral vs. ipsilateral)) confirmed that the mean N2 amplitude in a window from 250-325 ms was significantly modulated by the information conveyed by the number of arrows ($F(1,15) = 12.072$, $p < 0.001$). Post-hoc t-tests (Bonferroni adjusted alpha level: 0.025) demonstrated that the N2 was significant higher in the 1- compared to the 2- arrow condition ($t(15) = 4.465$, $p < 0.001$); however there was no difference between the 2- and the 3-arrow condition ($t(15) = 1.238$, $p = 0.235$). While there was an effect of Hemisphere ($F(1,15)=70.14$, $p<0.001$) due to higher N2 amplitude over the contralateral hemisphere (hence the EDAN), this did not interact with Cue information (i.e. Number of arrows).

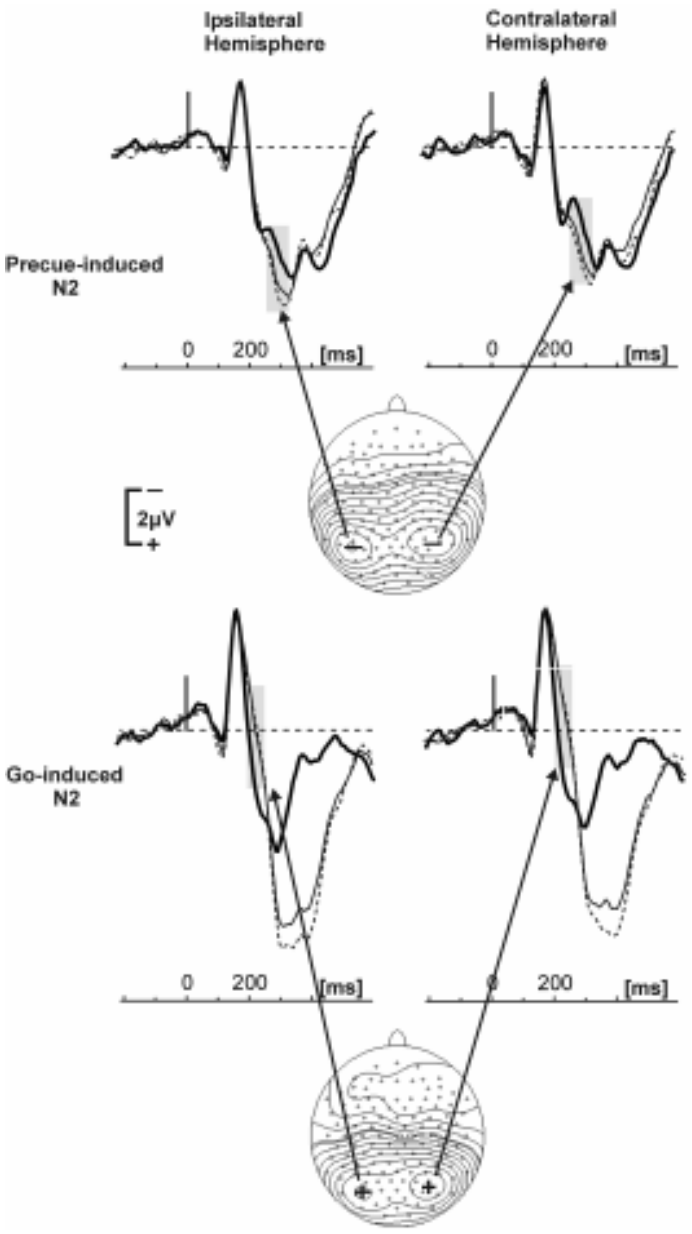

Figure 5.9: Waveforms and scalp distributions of the N2 component (pre)cue (top) and the imperative (bottom) signal. Left and right hand of the right hand conditions were transposed in order to map the combined left and right hand data on the left hemisphere (ipsilateral) and right hemisphere (contralateral). Waveforms represent data pooled from electrode sites (P3, P5, CPP5h and PP05h: ipsilateral) and (P4, P6, CPP6h and PPO6h: contralateral) The 1-, 2- and 3- arrow condition is represented by the thick solid line, the thin solid line and the thin dashed line,

respectively. The small vertical lines at time 0 correspond to the onset of the precue (top) and the imperative stimulus (bottom), respectively. The horizontal dotted line denotes the baseline.

If the higher amplitude N2 for the full compared to the partial-information cue conditions is related to the processing of spatial information for response selection, one may predict that the N2 elicited by the imperative cue will show the opposite amplitude relation between full and partial-information cue conditions. As shown in Figure 5.9, the N2 elicited by the response signal is more difficult to recognize due to a shorter latency, creating overlap with the N1. However, its topography (which resulted by subtraction the 3- arrow condition from the 1-arrow condition) was similar to the N2 elicited by the precue and its amplitude is modulated by cue information. Analysis (similar to the one performed for the precue-related N2) of the mean amplitude in a time window from 200-250 ms after the imperative cue onset confirmed significant effects of the directional information conveyed by the Number of arrows ($F(1,15)=28.333$, $p < 0.001$), as well as of Hemisphere ($F(1,15) = 15.401$, $p = 0.001$), as well as a significant interaction between the Number of arrows and Hemisphere ($F(1,15) = 5.442$, $p = 0.017$). Unfortunately, the effect of Hemisphere and the interaction with the Number of arrows cannot be studied any further due to temporal overlap with the much stronger lateralization of motor cortex activity (i.e. LRP), which dominated the EEG signal in this period. As previously, the effect of cue information conveyed by the number of arrows was due to a difference between full and partial-information conditions, there being no significant difference between the 2- and 3-arrow conditions (1 vs. 2-arrow condition $t(15) = -7.584$, $p < 0.001$; 2 vs. 3-arrow condition $t(15) = -0.582$, $p = 0.569$).

5.4. Discussion

The results of the present study showed that complete or partial information about the direction of a prepared reaching movement modulates electrophysiological components (i.e. CNV, LRP and ADAN), which develop during the foreperiod interval. The amplitudes of these components vary depending on the information provided by the precue stimulus. Corresponding results were recorded at the peripheral level, where reaction times decreased with the amount of prior information. These phenomena presumably reflect the presence of mutually suppressive interactions between neuronal populations in the primary and premotor cortex during response preparation. We first discuss this interpretation against the background of previous work and then consider parieto-frontal interactions on the basis of the modulation of parietal EEG signals.

5.4.1. Reaction Times

Reaction times (RTs) were inversely related to the number of response alternatives. Participants responded faster when the movement target was fully predetermined and slower when three potential targets were indicated by the precue stimulus.

The practice of employing reaction times measures in order to study motoric processes, which develop during the foreperiod of a precuing task, was first introduced by Rosenbaum in 1980. In that study, reaction times were becoming faster with the number of movement dimensions (i.e parameters such as direction, extent etc.) specified in advance by the precue stimulus (the movement precuing effect). Rosenbaum (1980)

attributed this effect to motor programming/specification of parameters which occurs in a hierarchical order before the response signal. According to this view the reaction times reflect the necessary time to specify the parameters, which were not precued. Goodman and Kelso (1980), on the other hand, argued that the precue information simply reduces the number of response alternatives. According to this view, the movement precuing effect arises at a stage before motor processing. However, later studies have consistently reproduced the phenomenon of reaction times' shortening due to increased information provided by the precue stimulus (e.g. Ulrich et al., 1998; Wild-Wall et al., 2003), regarding it, at least partially, as an effect related to motoric preparation (De Jong et al., 1988; Leuthold et al., 1996; Müller-Gethmann et al., 2000). The present study is different in the sense that we provided graded information about a single parameter (i.e. movement direction); however the scaled shortening of reaction times and the strong evidence of premotor and motor activation (discussed later in the text) is in agreement with Rosenbaum's view.

Our experimental design followed that of Bastian et al. (2003), where activation of primate's primary motor cortex varied as a function of the range of possible movement directions, which resulted to a corresponding scaling of reaction times. Those results point towards the existence of concurrent and mutually inhibiting representations of multiple potential actions; an assumption which forms the theoretical basis of the "affordance competition hypothesis" (Cisek, 2007).

It should be noted though that our design does not allow us to determine whether the scaling of reaction times was caused by the number of possible movement targets per

se or by the spatial angle (i.e. the length of the circular arc) in which the targets were located. The later view is supported by Bock and Eversheim's (2000) results, which showed that reaction times of reaching movements towards two or five alternative targets were the same when the targets subtended the same spatial angle. This result was accurately reproduced by a computational model implementing decision and spatial planning processes at the same level (Cisek, 2006). Manipulation of the number of potential targets within certain spatial angles would potentially help us resolve this issue in future experiments.

5.4.2. Graded premotor cortex activation

Cisek and Kalaska (2005) reported directionally tuned neuronal activity from primates' PMd prior to a precued reaching movement. Interestingly, when the primates were facing two potential targets, two concurrently developing and mutually inhibiting directional signals arose in the PMd. Competitive interactions between those signals led to narrower tuning functions and weaker activity for each peak and eventually slower reaction times. Analogous interactions recorded from primates' superior colliculus (Basso and Wurtz, 1998) can be detected in human visual areas in the form of suppressed fMRI signal (Kastner et al., 1998).

To evaluate scaling of movement-related EEG activity with number of response alternatives in the PMd, we relied on the ADAN ERP component, which peaked ~400 ms after the presentation of the precue stimulus and its amplitude was inversely related to the

number of response options. The ADAN reflects supramodal control of spatial attention (Eimer and van Velzen, 2002; Eimer et al., 2003b; Seiss et al., 2007), but is also elicited by the selection of the responding hand, even if no attentional shift is required (Praamstra et al., 2005). Gherri et al. (2007) demonstrated that the ADAN can also be elicited before reaching movements and is associated with effector as well as movement direction selection. It is most likely generated in the dorsal premotor cortex (Praamstra et al., 2005; Mathews et al., 2006), although small contributions from the frontal eye fields (FEF) cannot be excluded (Van der Lubbe et al., 2006). Moreover, the amplitude modulation of the ADAN is in agreement with the concept of competitive, mutually suppressive interactions between alternative simultaneously active movement representations. In addition, taking into account that the PMd has been shown to contribute to the generation of the CNV (e.g. Praamstra et al., 2006) as well as the pre-movement LRP (e.g. Mathews et al., 2006), the scaling of these components could be partially attributed to the competing activation of PMd neurons.

5.4.3. Graded primary motor cortex activation

The amplitude of the contingent negative variation (CNV) (Walter et al., 1964) was inversely related to the number of response options. Isopotential topographical maps (Figure 5.4) showed that the late CNV (i.e. during the last 200ms prior to the imperative stimulus) was stronger over central electrodes along the midline and towards the side contralateral to the prepared response. Previous studies have demonstrated that the CNV is generated by an extended thalamo-cortical-striatal network (e.g. Nagai et al., 2004;

Purzner et al., 2007). The CNV reflects anticipation of the imperative stimulus and most importantly response preparation originating mainly from premotor and primary motor areas (Macar et al., 1999; Leuthold and Jentzsch, 2001; Pfeuty et al., 2005; Praamstra et al., 2006). Asymmetric activation of the primary motor cortex (M1) becomes prominent during the late part of the foreperiod interval (Hamano et al., 1997; Rektor, 2000; Leuthold and Jentzsch, 2001; Gómez et al., 2003). This pattern of activation is reflected in the stronger CNV amplitude over the contralateral to the response hemisphere.

The presence of the lateralized readiness potential (LRP) prior to the imperative stimulus provides solid evidence for the contralaterally dominant activation of M1 (Praamstra et al., 1999). The LRP reflects the differential activity between the contralateral and ipsilateral motor cortex prior to the execution of a programmed response (for a review, see Eimer and Coles, 2003). Importantly, the task-induced scaling of the LRP amplitude was similar to the CNV scaling. The enhancement of the LRP as well as the CNV amplitude due to advance specification of movement parameters is a phenomenon attributed to motoric preparatory processes (Mackay and Bonnet, 1990; Vidal et al., 1995; Leuthold et al., 1996, 2004; Ulrich et al., 1998). Such results are interpreted (cf. Leuthold et al., 2004) as evidence in favour of the hierarchical view of motor programming, according to which parallel preparation of movement parameters (e.g. finger flexion and finger extension) would yield higher motor cortex activation, hence higher CNV and LRP amplitudes. The hierarchical model of movement organization, however, cannot explain the direction of the amplitude modulation of the CNV and the LRP components in our study and it also contradicts previous EEG studies. For example, Kitamura et al. (1993) reported lower amplitude of movement-related slow

brain potentials during preparation of single finger movements compared to preparation of simultaneous movement of two fingers.

Our results are remarkably similar to the ones reported by Bastian et al. (2003). The authors, by means of intracranial recordings from primates' primary motor cortex, demonstrated the preshaping and continuous evolution of the distribution of neuronal population activation (DPA), depending upon complete or partial specification of the direction of the upcoming reaching movement. The number of possible reaching targets indicated by the warning signal was related to the width and inversely related to the amplitude of the DPA of these motor neurons. Bastian et al. (2003) argued that the pattern and the time-course of M1 neuronal activation provided strong evidence for the existence of a neuronal mechanism where different movement options are processed in a tautochronous and continuous manner. In other words, all possible movement options (directions) were simultaneuously represented in distinct, directionally tuned MI neuronal populations; these representations were evolving in parallel during the entire foreperiod. Taking into account the analogies in experimental paradigm and results between Bastian's et al. (2003) study and ours, as well as the established motoric origins of the late CNV and the LRP, it is reasonable to argue that the task-induced scaling of these components is a manifestation of this mechanism at the scalp level.

5.4.4. Parieto-frontal interactions

An integral concept of the "affordance competition hypothesis" (Cisek, 2007) is that response selection and decision processes are mediated in the same neural substrate. According to this view, competitive interactions between representations of multiple potential actions take place in the fronto-parietal network, which in the case of visually-guided actions includes the dorsal premotor cortex (PMd) and the medial intraparietal area (MIP). The decision between alternative actions does not occur in a fixed order between parietal and frontal cortex, but it is influenced by the nature of the available information. Thus, decisions dependent on an abstract rule may be first implemented in frontal cortex, whereas the precue and response stimuli of the present study, providing direct sensory information, may enforce a decision in parietal cortex earlier than in the motor cortex (Cisek, 2006, 2007).

In the present study, the modulation of the posterior parietal N2 component preceded the frontally generated ADAN; however it just allowed the discrimination between full information and partial information conditions. In the case of full information precues, the parietal cortex identifies the required pointing direction and does not revisit the spatial information provided by the response signal. Conversely, in the case of partial information precues, the parietal cortex does not demonstrably take advantage of the reduction in uncertainty provided by the 2-arrow cue over the 3-arrow cue. Nevertheless, this modulation shows that the N2 reflects processing of spatial information for response selection rather than being merely related to visual processing (Van Velzen and Eimer, 2003).

It should be noted though that the lateralization of the N2, which was expressed as the EDAN component, was independent of cue information. This finding is unsurprising in view of the bilateral layout of the fronto-parietal network (Corbetta and Shulman, 2002), and underscores that lateralized potentials provide only a restricted view on its functional anatomy (Praamstra et al., 2005; Green and McDonald, 2008). The EDAN is exclusively elicited by visual cues (Eimer et al., 2002) and it is typically associated with the appreciation of spatial cues and the consequent redirecting of spatial attention (Harter et al., 1989; Hopf and Mangun 2000). The EDAN has often been labeled as a disguised N2pc component, which is associated to visual selection instead of the control of spatial attention (Van Velzen and Eimer, 2003). The current data are incompatible with this view, showing that the N2 underlying the EDAN is related to the extraction of spatial information from precue and response signals, which is unlike the functional interpretation and behaviour of the N2pc (Kiss et al., 2008).

It is also possible that the modulation of the N2 component and the invariability of its lateralized part (EDAN) between conditions reflect the output of the parietal reach region (PRR). The PRR comprises of multiple parietal areas; it is primarily located in the medial bank of the intraparietal sulcus (including the MIP area, Colby and Duhamel, 1991) close to the junction with the parieto-occipital sulcus (Snyder et al., 1997). PRR activity is related to decision making processes regarding reaching movements towards potential targets (Scherberger and Andersen, 2007). The most prevalent view about its functional role is the encoding of visual signals and their transformation into reaching plans (Snyder et al., 1997; Batista et al., 1999; Buneo et al., 2002). It is also possible that PPR neurons reflect the prospective encoding of motor intention even without the

presence of a driving stimulus (Cui and Andersen, 2007). Of direct relevance to our study, is the finding of Chang et al. (2008) regarding the existence of PRR neurons, which fire specifically before contralateral limb movements and independently of movement direction. Importantly, these neurons are not anatomically distinct from other PRR neurons, which are activated at the same time but independently of limb selection. Such neuronal activation patterns correspond with the modulation and the lateralization of the early parietal activity in our study. However, the question whether these phenomena are related to allocation of spatial attention and/or motor intention cannot be answered with certainty from the present data.

5.4.5. Interpretational limitations

Despite the remarkable correspondence between our results and above-mentioned studies on primates, certain issues might arise, which question the validity of the interpretation of our results. An alternative view of the scaling of movement preparatory activity is that participants simply engaged more in advance preparation of a response when more precise information was provided, hence producing stronger preparatory activity. In the absence of direct evidence for simultaneous representation of multiple movement directions in our data, this explanation cannot be entirely ruled out. However, this alternative explanation is not particularly plausible for the following reasons.

First, stronger preparatory activity and faster reaction times are correlated to increased neural firing rates (e.g. Riehle and Requin 1989; Hanes and Schall 1996).

However, such correlation depends on the directional preferences of the relevant cells (Riehle and Requin 1993). Accordingly, in Bastian et al. (2003) the overall neural activation alone did not discriminate between two- and three-arrow partial information conditions. Instead, a sharpening of the DPAs was observed when directional information was more precise and discriminated between two- and three-arrow conditions.

Second, higher amplitudes of pre-movement LRP are accompanied by faster responses. Appropriately, a relation with firing rate differences between fast and slow responses has been suggested (Coles 1989; Requin et al. 1991). However, analyses of the shape of the DPA in fast and slow trials by Bastian et al. (2003) demonstrated that fast trials are distinguished from slow trials by a narrower peak of the DPA, implying that it is an increase of directionally specific activity that gives fast trials their advantage.

Third, the representation of multiple movement directions in primate motor and premotor cortex occurred without there being a need to use the precue information; i.e. the monkeys could have waited with the planning of a movement until the go signal (Bastian et al. 2003; Cisek and Kalaska 2005). Similarly, human participants in movement precuing tasks demonstrate lateralized movement preparatory activity as a function of precue information even if it is not required to use that information (Leuthold et al. 1996; Ulrich et al. 1998).

Together, these points convincingly support the view that the experimentally induced amplitude modulation of ADAN and LRP is not a nonspecific effect of variation in effort, but instead a specific effect of the manipulation of directional information.

5.5. Summary

The present study demonstrated that the amplitudes of EEG components, which originate from the dorsal premotor and the primary motor cortex are scaled depending on the information provided by the precue signal regarding a single movement parameter (i.e. reaching direction). Our results are in agreement with the predictions of the affordance competition hypothesis proposed by Cisek (2007), according to which, encoding of movement direction and response selection are processed within the same neural network. Central in the function of this network are the reciprocally interconnected dorsal premotor and posterior parietal cortices, the order of activation of which depends on the nature of a task. However, irrespective of the order of activation, multiple directional options are eventually represented in PMd neuronal populations. Due to the mutually-inhibiting nature of these representations, PMd activity decreases with the number of reaching options. We believe that this mechanism was reflected in our study in the scaling of the ADAN amplitude. It should be noted though that Cisek (2006, 2007) assigns a less significant role to M1, because of the stronger competing interactions between M1 neuronal populations, which presumably would not allow the presence of multiple directional signals (Cisek, 2006). However, interactions between directionally tuned MI cells have been reported earlier (Georgopoulos et al., 1993). Moreover, Bastian et al. (2003) have clearly demonstrated the existence and parallel evolution of multiple directional signals in M1 neurons whose amplitude was inversely relate to the number of possible movement options, a finding that corresponds with the amplitude scaling of the motoric components in the present study (i.e. LRP and late CNV). Our results suggest that preparation for reaching movements towards multiple potential targets triggers

tautochronous and competing directional tuning of neuronal populations in the dorsal premotor and as well as in the primary motor cortex.

Chapter 6

General Discussion

6.1. Summary

In the present thesis we studied the properties of EEG components, which develop prior to a cued or a conditioned response in order to shed light on the neural processes that govern preparation for action. For this purpose, we examined the time course and the amplitude modulation of event related potentials, in particular slow brain and lateralized potentials mostly associated to premotoric and motoric processes. A substantial part of this work consisted of the study of oscillatory phenomena in motor control, either frequency-specific modulation of intrinsic brain rhythms or steady-state responses to peripheral electrical stimulation. In addition, we applied a range of source localization techniques with the aim of overcoming the inherent limitation of EEG regarding the "inverse problem" (see Section 1.2.1.2.) and propose, where possible, new methods in EEG data analysis.

In the first two experimental chapters we asked questions regarding the neural mechanisms underlying temporal preparation and the effects it has on post-movement neural processes as well as on peripheral outcome. In particular, in Chapter 2 we examined the neural correlates of implicit timing, in a task where the unintentional representation of a time interval was dictated by the periodic presentation of visual stimuli. In Chapter 3, we quantified the differences between time-based motor planning and general motor anticipation in a task where participants responded to periodically or randomly applied external loads.

In Chapters 4 and 5 we dealt with the other aspect of phasic action preparation, which is referred to by with the term "event preparation". In Chapter 4 we examined the

preparatory processes associated with the selection of the responding hand as revealed by the interaction (at the source level) between steady-state somatosensory responses and motor-related lateralized event potentials. Finally, in Chapter 5 we investigated the preparation for multiple movement options as realized in the primary motor cortex and the fronto-parietal network.

6.2. Temporal preparation

Temporal information provided by external stimuli in combination with memory of the timing of past events has a dominant effect in the organization of behaviour and the optimal interaction with the surrounding environment. In the case of an external event occurring at a predictable point in time, temporal expectation can occur in a controlled/intentional and/or an automatic/unintentional way. In the former case, a person has been made aware of the timing of an upcoming event (often referred as "temporal orienting", Coull et al., 2000), whereas in the latter case temporal preparation relies on the temporal pattern of the events preceding the current event (often referred as "trace conditioning", Los et al., 2001). Temporal orienting is typically studied using the movement-precuing paradigm (see Section 1.6.1.), while trace conditioning by manipulating the interstimulus interval (Los and Heslenfeld, 2005).

The experiment described in Chapter 2 fits well with the definition of "trace conditioning". There, the participants were unintentionally representing the length of the time interval between successive imperative stimuli, while performing a choice-reaction

task with no apparent temporal requirements or restrictions. The temporal encoding was reflected in two "Pavlovian responses"; the termination of the rise of the CNV slope and the alpha Desynchronization in the absence of an expected stimulus. The study in Chapter 3 however, shares elements of both "trace conditioning" and "temporal orienting". In that experiment, although the temporal entrainment of the participants took place through the periodic presentation of external loads, the correct performance of the task required from the participants to intentionally time their response with the occurrence of the external load.

The difference between implicit and explicit timing processes may well be reflected in the difference in the scalp distribution of the slow brain potentials recorded in each task. In Chapter 2 the topographical maps agreed with the results of the source localization method we employed (i.e. minimum norm approach) for lateral, possibly dorsal, premotor cortex origins for the late CNV. On the contrary, in Chapter 3 the scalp topography of the slow-rising negativity, which shares elements with both CNV and BP components, clearly suggested activation of the supplementary motor area (SMA) with contribution of the primary motor cortex (MI) close to load onset.

It is recognized that the neural networks involved in motor timing tasks are modality-specific (Jäncke et al., 2000; Jantzen et al., 2005). Furthermore, it has been also suggested that any cortical network is intrinsically capable of temporal processing (Buonomano, 2003). Jantzen et al. (2007) stated that timing processes in a coordination task are mediated by basic sensorimotor networks. In accordance with our findings, the authors showed that the SMA is part of a network whose activation is related to the

explicit timing requirements. SMA activation is a common theme in explicit representation of time (e.g. Rao et al., 2001; Macar et al., 2002; Pfeuty et al., 2005). We are not claiming though that the SMA activation in Chapter 3 solely reflects the encoding of the duration of the interval between two successive external loads. As discussed in Section 1.6.1.4, the SMA is involved in motor preparation and execution, which was evident from the force as well as the EMG measurements showing that there was a gradual build-up of pre-load muscle activation. Our results show that when anticipating a periodically applied external load, these processes operate in an explicitly defined temporal frame.

Often, SMA activation is accompanied by lateral premotor activation especially in tasks requiring extraction and prediction of sequential information and retrieval of temporal information from memory (Mushiake et al., 1991; Schubotz and von Cramon, 2003). In addition, Jantzen et al. (2007) argued that lateral premotor cortex activation (along with pre-SMA activation) is not related to the processes specific to motor output but rather represents the temporal information during pacing and coordination. Such notion agrees with our findings in Chapter 2 regarding the implicit representation of time intervals. A noticeable difference, however, between our study and other timing tasks is the absence of medial premotor activation. Although the precise neural mechanisms cannot be elucidated in our analyses, it is possible that this discrepancy was due to the nature of our task, especially since distinct brain structures are involved in tasks with different timing requirements (e.g. automatic vs. cognitively controlled, Lewis and Miall, 2003; rhythmic vs. discrete, Schaal et al., 2004).

One might argue that the differences in preparatory activity between tasks arose from the lack of motor activation in the implicit timing task. Since the specific response finger was unknown, it would be an adequate strategy for the participants to refrain from any motor preparation. However, the analysis of the beta activity modulation demonstrated that that was not the case. The contralateral to the response hand hemispheric predominance and also the spatiotemporal overlap of beta ERS on a given trial with the beta ERD preceding the following trial provided strong evidence for primary motor cortex activation prior to stimulus presentation.

In addition to premotor and primary motor areas, activation of parietal as well as occipital areas was modulated due to the temporal pattern of the driving stimuli. The finding that the parietal cortex contributed to CNV generation was surely not unexpected based on the role of the superior and inferior parietal lobules in time perception (e.g. Rao et al., 2001; Coull et al., 2004). The involvement of the occipital cortex, as demonstrated by the modulation of alpha activity, to our knowledge, has not been previously reported in implicit timing tasks. Occipital alpha ERD is typically associated to allocation of visuospatial attention and facilitation of visual stimuli processing (Fries et al., 2001; Van der Togt et al., 2006; Thut et al., 2006; Bauer et al., 2006). Moreover, a predictable spatio-temporal pattern of visual stimuli induces perception orientation of the visual system, allowing it to extract relevant information from the environment (Guo et al., 2004, 2007). Accordingly, the presence of alpha ERD in our experiment at the time of the expected stimulus probably signifies facilitatory processes of visual processing. On this basis, we would expect increased visual evoked responses following stimulus presentation; instead, we observed the opposite. It is possible that evoked responses

depend more on the phase locking rather than the amplitude modulation of the oscillatory rhythms (Hanslmayr et al., 2007); nevertheless, the discrepancy between pre- and post-stimulus activity requires further research.

In Chapter 3, on the other hand, the relationship between pre- and post-load activity was of central interest to us. Analyses of motor-related slow brain potentials, beta ERD, as well as peripheral measurements (i.e. grip force and muscle activity) leave no doubt about the existence of preparatory processes that took place when the participants were facing external loads with a regular, thus predictable, time regime. These processes reflected the reduction of uncertainty regarding the temporal occurrence of an external load. Consequently, the participants adjusted their grip, which in turns led to a decreased amplitude of the long latency reflex (LLR), which was induced by the rapid, vertically applied external perturbations. Interestingly, the LLR was preceded by motor activity which was correspondingly modulated by the (un)predictability of the perturbations. The latency of this component (termed N58-P58 component) made it a potential candidate for the presumed LLR cortical generator.

Admittedly, a weakness of this study was the large width of the manipulandum, which resulted in rather imprecise EMG measurements. This could also have been the reason for not being able to establish a correlation between the N58-P58 and the LLR amplitude, which would have pointed towards a causal relationship between these components. Nevertheless, the primary motor cortex origins of the N58-P58 component (as elucidated by our successful source analysis) argue in favour of the cortical control of the LLR. The LLR is believed to reflect coordinated control of different muscles (Gielen

et al., 1988), approximating patterns normally used for voluntary movements (Hasan, 2005). This functional overlap could be caused by a shared neural substrate between reflexive and voluntary motor control (Kurtzer et al., 2008). This notion is consistent with recent concepts of optimal feedback motor control, according to which internal models utilise adaptable feedback gains in order to face multiple and often competing task requirements (Todorov and Jordan, 2002; Scott, 2004).

6.3. Event Preparation

In the first two experiments we investigated the neural correlates of volitional and automatic representations of time intervals during preparation for action and their effects on neural and behavioural responses. In the second part of this thesis, we examined the neural correlates of preparing for execution of a specific response. In both tasks (discussed in Chapters 4 and 5) we employed the movement-precuing paradigm with a fixed interstimulus interval, which is a standard way of studying event preparation processes. Evidently, in such experimental designs there is a strong element of temporal preparation; however, we chose to focus on the response selection and execution processes rather than the timing of the response.

The experiment described in Chapter 4 had a strong methodological aspect. We addressed a simple question regarding the mechanisms of action preparation by studying the interaction between movement-related lateralized components (ADAN, LRP) and steady-state somatosensory evoked potentials (ssSEPs), known by the term “sensorimotor

gating". In this study, in order to overcome the uncertainty regarding the origins of scalp-recorded activity, we proposed a new method of analysis, which consisted of ssSEP source localization and statistical assessment of sensorimotor gating at the source level.

The source localization method (described in details in Chapter 4) revealed two dipole sources oriented along fronto-occipital meridians and located (on average) posterior and close to the central sulcus, most likely in the primary somatosensory cortex (SI). Intracranial recordings from primates (Mountcastle et al., 1969) have demonstrated the responsiveness of SI cells to mechanical vibrations in a wide range of frequencies. Comparable results have been obtained by regional cerebral blood flow imaging (Fox et al., 1987) and source localization methods using EEG (Snyder, 1992) and MEG (Pollok et al., 2002; Nangini et al., 2006). Regarding the physiological mechanisms of ssSEP generation, it is still not clear whether the ssSEPs arise from superimposition of transient SEPs (Pollok et al., 2002) or from neighbouring however distinct cortical areas. In the former case, precentral contributions cannot be ruled out (Snyder, 1992), especially considering the debate about pre- or post-central origins of certain transient SEPs (e.g. Waberski et al., 1999; Huang et al., 2000). Additional contributions from the secondary somatosensory cortex (SII) are also possible (Snyder, 1992), although SII cells have been shown to respond mostly to high frequencies (> 50Hz, Burton and Sinclair, 1991).

Sensorimotor gating at the source level has been studied previously, investigating transient SEPs' modulation during active and passive movements (Valeriani et al., 1999). Extending these findings, we studied sensorimotor gating during preparation for action using the steady-state SEP approach as a continuous probe of response selection

processes. Our results point towards premotor cortex contribution to premovement attenuation of sensory signals, since the ssSEP amplitude reduction coincided with the occurrence of the ADAN component (for the premotor origins of the ADAN, see Section 1.8.4.2). Support for our claim comes from a TMS study, where it was demonstrated that sensory attenuation is caused by premotor efferent motor signals (Voss et al., 2006). Moreover, the attenuation of the ssSEPs was stronger in the hemisphere contralateral to the response hand, which, in agreement with the majority of previous studies (see Section 1.8.4.2), suggests that the ADAN results from activation of the contralateral PMd reflecting the selection and/or covert activation of a motor response.

In Chapter 4 we proposed a novel type of analysis of sensorimotor gating in order to address questions regarding the preparatory neural processes in a simple choice-reaction task. On the contrary, in Chapter 5 we followed a "straightforward" way of analysis for asking a more complex question with regard to the neural mechanisms of preparation for action when a person faces multiple movement options. Resembling more of a real-life scenario, the participants were facing variable levels of uncertainty regarding the location of a reaching target. The condition where the target was fully specified by the precue stimulus was similar to the experiment in Chapter 4; of particular interest were the cases where the participants had to prepare a reaching movement towards two or three equally probable target locations.

The formation of a decision to act is traditionally viewed as organized through a series of steps. These include collection of sensory input and integration with reward expectancy and cognitive information, weighing of options in combination with previous

experience, response selection and execution of the selected movement (for a review, Opris and Bruce, 2005). Cisek (2006, 2007) on the other hand, argued that action selection and specification of movement parameters occur in parallel and within the same neural substrate. In his model, (spatial) decision making takes place in a fronto-parietal network comprising the dorsal premotor cortex (PMd) and the posterior parietal cortex (PPC), which receives biasing input from the prefrontal cortex (PFC) and finally projects its output to the primary motor cortex (MI). Certain reservations arise from the lack of information regarding the possible contribution of other premotor areas directly connected to MI and the rather unspecified role of the PFC (Bestmann, 2006). Nevertheless, Cisek's (2006, 2007) model manages to replicate previous findings from primates (Cisek and Kalaska, 2002, 2005) and behavioural (Bock and Eversheim, 2000) studies.

Our results are compatible with Cisek's predictions in terms of direction-dependent, scaled PMd activation (i.e. ADAN), which was accompanied by activation of the PPC (i.e. N2 and "EDAN"). In fact, parietal activation preceded premotor activation possibly because the decision to act was based on sensory features of the stimuli (Cisek, 2007). According to our findings, the PPC initiates the processing of spatial information, but without discriminating between the conditions of partial information. The full discrimination takes place initially in the PMd, where all possible movement options are encoded in a mutually suppressing manner. In addition, contrary to Cisek's (2006, 2007) model, we also found evidence in the form of scaled LPR and CNV components, that this information is passed to and sustained in the MI (see also Figure 5.7). Previous single-cell studies have reported preparatory directionally-specific activation in primates' PMd

as well as in MI (Riehle and Requin, 1989; Shen and Alexander, 1997a, b), whereas Bastian et al. (2003) have provided solid evidence for the coexistence of preparatory activity for multiple directional options. In agreement to these studies, our results indicate that the role of MI in response selection and specification may be more important than assumed by Cisek (2006, 2007).

There are however a few remaining questions not addressed by our study. For instance, it is not clear whether the scaling of PMd and MI activity is caused by the number of the potential targets or the spatial angle that they define, as suggested in reaction time experiments (Carson et al., 1995; Favilla, 1996; Bock and Eversheim, 2000). Varying the number of reaching targets within a certain spatial angle would potentially provide the answer to this question. It is also noteworthy that in motor control literature there is a prevalent notion that discrete preparation for multiple targets can only occur when the targets are separated by at least 60^{o} of spatial angle (Ghez et al., 1997). Our results showed that this is not accurate since the targets in our experiment were just 45^{o} apart. Clarification of this issue can be achieved by varying the degrees of spatial separation between targets.

Besides questions that can be resolved by simple modifications of the task metrics, more detailed investigation is needed about other issues, which are related to more fundamental questions regarding the relationship between neural firing and motor output. It is not clear, for example, which is the reference frame through which the visual information is transformed to muscle contraction. Batista et al. (2007) reported that in the PMd and the MI, some groups of neurons encode reaching plans in eye-centered

coordinates, while other groups in hand-centered coordinates and other groups in both, which raises the possibility that PMd and MI neurons utilize an intrinsic frame of reference or perhaps have no reference frame at all (Wu and Hatsopoulos, 2006, 2007).

Another intriguing issue has to do with the relationship between neural activity in premotor and motor cortices and movement parameters. Although PMd and MI neuronal populations do seem to encode time-invariant movement features (e.g. direction and distance), recent evidence suggest that non-spatial parameters, such as speed of movement, have a measurable effect on neural preparatory activity (Churchland et al., 2006). Todorov (2000) offered an alternative or perhaps complementary view of the MI neurons' functional role, proposing that it is the low-level movement features (e.g. endpoint kinematics) that are represented in neuronal activity. Although this view has raised a certain amount of controversy (see, Moran and Schwartz, 2000; Georgopoulos and Ashe, 2000), it does not contradict neuronal representation of high-level movement features, but it delineates an additional causal relationship between MI neuronal firing and activity of individual muscles (Scott, 2000).

More recently, it was suggested that the temporal complexity and heterogeneity of single PMd and MI neurons' response patterns may indicate that movement parameters are correlated to but not specifically represented in neuronal activity (Churchland and Shenoy, 2007). Instead, single neurons could form a recurrent network whose purpose is the generation and the control of movement via production of temporally patterned outputs. The temporally complex nature of MI neurons has been encapsulated in an elaborate model proposed by Hatsopoulos et al. (2007), according to which MI activity is

correlated (although no causal relationship is established) with temporally-dependent movement trajectories (termed "motor fragments" or "pathlets"). The authors also argue that MI neurons encode complex kinematic trajectories rather than complex kinetic trajectories as proposed by earlier studies (Sergio and Kalaska, 1998; Sergio et al., 2005). This discrepancy could be due to the fact that Hatsopoulos et al. (2007) recorded activity from the rostral part of the MI, which has been related to kinematics encoding (Ashe and Georgopoulos, 1994; Crammond and Kalaska, 1996).

6.4. Concluding remarks

Electroencephalography was employed in the present thesis in order to elucidate the evolving neural mechanisms during preparation for action. "Traditional" transient ERP analyses were complimented by analyses of the modulation of intrinsic brain oscillations, of oscillatory responses driven by periodically applied external stimuli and also of various source localization methods. Quite often, our results exhibited a significant correspondence with findings from intracranial studies and imaging methods. Understanding of the brain mechanisms of motor control can only be achieved by acknowledging the inherent limitations of each recording or imaging technique and combining their respective advantages off- or even on-line when possible. In addition, EEG can be used for the benefit of several patient populations. For example, Praamstra and Pope (2007) assessed Parkinsonian patients using the paradigm described in Chapter 2, demonstrating that EEG phenomena related to implicit timing processes were absent in this patient group. Another fascinating application is the employment of single-trial EEG

in order to use the modulation of movement-related preparatory EEG components as a basis over which reliable brain computer interfaces (for a review, Birbaumer and Cohen, 2007) could assist people with severe motor disabilities operating computers (Pfurtscheller et al., 2006) and even artificial prosthetic limbs (Fagg et al., 2007) through motor imagery. In conclusion, EEG is an essential tool in revealing the dynamic neural processes which take place during preparation for action; we believe that the findings of the present thesis contribute towards the achievement of this goal.

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